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ORIGINAL COMMUNICATION

The outcome spectrum of multiple sclerosis: disability, mortality, and a cluster of predictors from onset

Helen Tedeholm · Bengt Skoog · Vera Lisovskaja · Björn Runmarker · Olle Nerman · Oluf Andersen

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Abstract Interest in the long-term natural history of multiple sclerosis (MS) is being revived, as disability endpoints become increasingly important with the advent of highly efficacious long range but potentially harmful drugs. MS had an increasingly benign course, probably due to better assessment and changing diagnostic criteria. Incidence cohorts reduce inclusion bias, capturing both extreme benign and severe cases. We conducted a 50-year follow-up of an incidence cohort of Gothenburg residents with MS onset in 1950–1964 ($n = 254$; 212 with an initial relapsing-remitting course and 42 with a monophasic course, diagnostic criteria according to Poser). Patients were followed longitudinally until censoring, death, or study termination in 2012 and evaluated using Kaplan–Meier estimates and Cox regression analysis. Median time to secondary progression was 15 years. Median time to EDSS6 and EDSS7 was 26 and 48 years ($n = 254$), respectively. The cumulative risk of reaching EDSS6 was 50 % at 55 years of age and 80 % at 80 years of age ($n = 212$). A score based on a cluster of clinical features at onset predicted secondary progression, EDSS6, EDSS7, and EDSS10 (hazard ratio 1.6–2.3 per score unit for women, 0.99–1.49 for men). This score predicted the disease course during five decades indirectly, by predicting time to secondary progression. Age at onset predicted the course in men, with 3–6 % yearly increase in the risk of reaching disability milestones. The present incidence cohort provided hard outcome data in untreated patients over several decades.

Keywords Multiple sclerosis · Natural history · Prediction · Prognosis · Gender · Age

Introduction

Consensus on the long-term outcome of untreated multiple sclerosis (MS) in terms of progression and disability is important as new but potentially hazardous therapies radically modify the course of MS [9, 49]. The proportion of progressive cases was initially studied using descriptive statistics [30]. Subsequent studies on the natural history of MS have had a geographical base and used Kaplan–Meier estimates of prognosis [12, 13, 17, 40, 46, 51]. In addition, patients with a primary progressive (PP) course were separated from attack onset patients [22]. The rate of secondary progression (SP) was similar to that of primary progression [12] and independent of the previous relapsing–remitting (RR) course [15, 53]. Age, rather than duration, was observed to predict the point of transition to SP and the subsequent accrual of disability. Several authors constructed an estimation of the distribution of age at SP without censoring, rather than employing a Kaplan–Meier estimate [11, 12, 39, 50]. The basis for natural history

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H. Tedeholm · B. Skoog · B. Runmarker · O. Andersen (✉)
Section of Clinical Neuroscience and Rehabilitation, Institute of Neuroscience and Physiology, the Sahlgrenska Academy, University of Gothenburg, Gröna Stråket 11, 3tr, Sahlgrenska Universitetssjukhuset, 413 45 Gothenburg, Sweden
e-mail: oluf.andersen@neuro.gu.se

V. Lisovskaja · O. Nerman
Department of Mathematical Sciences, Chalmers Technical University, Gothenburg, Sweden

V. Lisovskaja · O. Nerman
Department of Mathematical Sciences, University of Gothenburg, Gothenburg, Sweden

studies was recently broadened by larger international databases [16]. A recent study on prognosis was based on a large database of patient-reported symptoms [18].

Here, we present a 50-year follow-up of the natural history of the Gothenburg Incidence Cohort (GIC). An incidence cohort study describes the follow-up of population-based materials with a strict temporal window of inclusion [34]. This reduces inclusion bias, which strongly influences outcomes. The natural history of MS was previously evaluated in the GIC with 25 years of follow-up [15, 35]. The 50-year outcome of monophasic "CIS only" cases [32] and non-progressive cases [41] has also been reported, which was extended to include progressive cases in the present report.

Patients and methods

Patients

The GIC is a population-based incidence cohort of 305 MS patients who were residents of Gothenburg when they experienced their first symptoms of MS between January 1, 1950, and December 31, 1964. Incidence and prevalence studies for the period 1950–1964 were started simultaneously in this area. The Department of Neurology at Sahlgrenska University Hospital was the primary neurological service for the pre-defined catchment area, the city of Gothenburg ($N \approx 400{,}000$) [5, 7, 15, 32, 35, 41, 43]. A record of Gothenburg patients with acute optic neuritis was obtained from the Department of Ophthalmology at Sahlgrenska University Hospital and they were included in the cohort. Fifty percent of patients with initial relapsing–remitting (RRMS) were seen at onset, and 72 % of patients were seen within 3 years of their initial symptoms [35]. A few patients who were examined during the 1970s were included in the GIC because their onset was determined to be within the incidence period; we consistently prioritized the requirements for an incidence cohort and accepted combined retrospective-prospective recordings. Time to the endpoints, secondary progression, and Expanded Disability Status Scale (EDSS) 6 did not differ between incidence cohort cases seen at onset and incident cohort cases traced and included at their second event or later [35]. No differences were found between the incidence rates for patients with MS diagnosis according to Poser in the three 5-year incidence periods (1950–1954, 1955–1959, 1960–1964; 4.3, 4.2, 4.3/100,000/year) or for possible MS (1.1, 1.3, 0.9/100,000/year) [43]. Few patients from the incidence cohort were lost during the 50 years of follow-up; censoring was mainly due to death from other diseases or study termination by 2009–2012 (Table 1). Personal follow-up examinations continued until 2013. The number of patients in the incidence cohort was 309 in previous GIC reports [5, 41] and 305 in the present study. The diagnosis was changed in four patients, one with recurring neuromyelitis optica confirmed at autopsy, one with polyfocal microvascular disease detected at autopsy, one with bilateral optic neuropathy with severe sequelae considered to be Leber's disease, and one with a disabling polyneuropathy (probably Charcot–Marie–Tooth's) precluding the evaluation of probable concomitant mild MS. In the GIC, 212 patients had an initial relapsing–remitting course and MS diagnosis according to Poser: 42 had a clinically isolated syndrome (CIS) unequivocally suggestive of MS but with no further neurological disease activity and 44 had primary progressive MS according to Poser. Seven patients had a primary progressive course not strictly fulfilling the Poser criteria and were excluded from the present study resulting in a data set of 298 patients. The frequency of neurological examinations performed by the research team during the first 25 years of follow-up was published previously [35]. The number of team examinations in 227 survivors after year 25, in addition to regular examinations, was 815. None of the patients underwent any disease-modifying therapy. Azathioprin was never extensively used in Sweden. When interferon beta was introduced 1995, indicated for active relapsing–remitting disease with at least two relapses during the preceding 2 years, the GIC patients were either in a stationary phase with infrequent relapses or in a chronic progressive phase. A small number of relapses were treated with short courses of ACTH.

The following patient subsets were created: (1) RR-SP ($n = 212$), patients diagnosed with MS according to Poser with an initial RR course with or without transition to an SP course; this definition has been used in most natural history studies and enables comparisons with other natural history studies; (2) RR-SP-CIS ($n = 254$), patients diagnosed with MS according to Poser with an initial RR course (subset 1) or as "CIS only" with one episode unequivocally suggestive of MS but no further neurological activity ($n = 42$). This definition is adequate for studies involving prediction from onset; (3) PPMS ($n = 44$), patients diagnosed with MS according to Poser with a primary progressive course.

One patient was an Italian immigrant, and all other patients were of Scandinavian descent. The GIC includes a surplus of individuals with the DR15 type, as expected for MS patients, but the HLA type did not, or only marginally, influence prognosis in the GIC [37]. This study was approved by the medical ethics board of Gothenburg, Sweden, and was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments.

Table 1 Number of patients in the Gothenburg Incidence Cohort with certain demographic and clinical factors

	Men	Women	Total
Patients	120	185	305
PPMS	27	17	44
Possible PPMS	4	3	7
Attack onset	89	165	254[a]
CIS only	14	28	42
RR onset of CPMS/CDMS	75	137	212
CPMS/CDMS (Poser)	102	154	256[b]
Transition to SPMS	65	111	176
Censored for EDSS 10	65	119	184
Death from MS (strictly EDSS 10)	44	51	92
Death from MS EDSS10var	57	67	121[c]
Censored for death from other diseases	33	34	67
Malignant diseases	10	9	19
Vascular	16	16	32
Other	7	9	16
Censored: other disease prevents evaluation	10	21	31
Final follow-up 2009- (administrative censoring)	13	39	52
Censored: incomplete follow-up	9	25	34
Alive at last personal follow-up 2012	10	33	43
CIS only	2	9	11
Non-progressive	4	9	13
Sec. progressive	4	14	18
Prim. progressive	0	1	1

PPMS primary progressive MS, *CIS* clinically isolated syndrome, *CPMS* clinically probable MS, *CDMS* clinically definite MS, *EDSS* expanded disability status scale

[a] 212 CPMS/CDMS patients with initial RR course + 42 CIS only

[b] 212 RRMS + 44 PPMS

[c] Includes 29 patients with competing causes of death, from MS and another serious disease

Definitions

Secondary progression (SP) was defined according to established criteria as continuous (insidious) progression for at least 1 year, without remission, detectable at time intervals of months or years [26]. The probable year of transition to SP was determined after 1 year of observation. In the present study, SP conversion was recorded at the first unequivocal indication of insidious progression in any functional system [24]. SP will generally be notified earlier in the GIC than in cohorts where the transition to SP is defined by motor systems. A relapse was defined as new MS-related symptoms appearing within a time frame of days or weeks. Three dichotomous characteristics of the onset attack were evaluated based on reported definitions and predictive power [36]: monofocal symptoms (yes/no), afferent symptoms (yes/no), and complete remission (yes/no). Monofocal was defined as the absence of evidence of involvement of more than one neuroanatomical region, as determined by neurological examination. The term afferent referred to lesions in afferent tracts from the skin, muscles, eye, or labyrinths. Afferent relapses included optic, sensory, and vestibular symptoms, provided a documented lack of major efferent symptoms, such as central paresis. Parahypesthesia with hyperreflexia without paresis was recorded as afferent. Complete remission was defined as the absence of any persistent residual symptoms in the appropriate functional system as evaluated after the attack remitted, at the latest 1 year after the onset of the relapse. However, intermittent symptoms were allowed, and a Babinski sign at a later visit was not classified as incomplete remission. These criteria have been applied consistently in studies based on the GIC and were adapted into the Swedish national MS register by 1995 [3, 5, 15, 36, 44]. Similar predictors were tested in other natural history studies [2, 21, 25, 54]. Disability was evaluated by the EDSS [24]. The onset attack was classified as "distinct" ($n = 194$) or "indistinct" ($n = 18$) according to GIC definitions [5, 15]. Indistinct attacks were insidious but remitting ($n = 4$), vague, intermittent ($n = 4$), slowly evolving but remitting ($n = 8$), or pseudoattacks from a new focus ($n = 2$). "Second event" was either a relapse following the onset attack or the onset of SP. The second event defines the time of MS diagnosis; in a few cases, when the second relapse did not provide evidence of dissemination in space, resulting in a Clinically Probable MS (CPMS) diagnosis according to Poser, new foci often changed the final diagnosis to Clinically Definite MS (CDMS). In the category "CIS only", we included patients who had only one attack unequivocally suggestive of MS during a lifetime [32]. Structured information on

demographics, attacks, predictors, course, and disability, as well as concurrent diseases is the key content of the GIC database.

Mortality

We obtained death certificates from The National Board of Health and Welfare using the 10-digit national identification number of each patient. Of the 305 patients, 188 had died by 2012 when the study was terminated. Ninety-two patients had died from MS (usually with pneumonia as the immediate cause of death) and 29 from a combination of MS and other serious diseases. In 67 patients, MS did not contribute to their death. Fourteen who died from MS and 11 who died from other diseases before 1975 had only 6 digits in their identification numbers; for these 25 patients, death certificates were not obtained and data on the cause of death had to be obtained from the present GIC database and clinical records. Each case was evaluated by two of the investigators (HT and OA). Death from MS was classified as EDSS10 [24]. When both MS and another serious disease contributed (about equally) to the cause of death, we recorded the outcome as the EDSS10 variant (EDSS10var). A precondition for assigning patients to death from MS (including EDSS10var) was that the patient had previously reached EDSS7. Censoring was often a consequence of death from other diseases (Table 1).

Statistical analysis

Kaplan–Meier (K–M) estimates of time from onset to second event, SP, EDSS6, EDSS7, EDSS10, and EDSS10var were calculated for the RR-SP and RR-SP-CIS subsets.

The distributions of age at second event, SP, EDSS6, EDSS7, EDSS10, or EDSS10var were examined for the RR-SP subset using four different approaches with estimates from birth, as no established convention exists to calculate age at outcome:

1. We assumed that the endpoint of interest (e.g., SP), if not reached, occurred extremely late in a patient's life (censoring set to 100 years of age). This provides a maximum estimate of the age reached at the selected endpoints (a).
2. Censoring was performed as in the K–M estimate of time from onset (b).
3. All censored events were treated as if they reached the respective endpoints shortly after the censoring point, providing a minimum estimate of the age at the different endpoints (c).
4. Only patients who reached the endpoint were considered and a distribution estimate of ages constructed, without including censored cases (d).

By definition, all patients will reach the selected disability endpoints with approaches a, c, and d. The estimates obtained in a and c reflect the effect that censoring may have on the K–M estimate of survival given by b, encompassing the hypothetical, true empirical age distribution that would have been observed in the data if no censoring was present. The approach in d, the distribution estimate without censoring, enables comparisons with other cohort studies [11].

Univariate predictions of time to the endpoints SP, EDSS7, and EDSS10 were made with K–M estimates in the RR-SP-CIS subset. Each of the potential predictors (gender, age at onset, and the three dichotomous onset attack characteristics) and its predictive capacity were examined using a log-rank test. The only continuous variable, age at onset, was divided into two categories: age at onset $\leq$30 and >30 years.

For the multivariate analysis, we attempted to construct Cox regression models describing time from onset of the disease to four of the endpoints (SP, EDSS6, EDSS7, and EDSS10var) with the three dichotomous onset attack characteristics, gender, and onset age as explanatory variables. We fitted these Cox models to the total 50-year follow-up using models that provided the best penalized fit to the data, evaluated with Akaike information criterion (AIC). However, the resulting models did not fulfil the assumption of the proportionality of hazards required for the Cox models, indicating that different models were required for different times to endpoint. Moreover, multiple interactions involved gender, onset age, and the three dichotomous attack characteristics. When favourable (or the complementary unfavourable) predictors were retrieved from the MS onset data, different interactions appeared for different cut-off times. We highlight one of these strong interactions between gender and onset age with K–M estimates of time to SP constructed for stratification of data on age and gender. In order to stabilize the models and facilitate comparisons between endpoints we decided to change the modelling approach as follows.

First, we used the number of relapse-associated predictors as a severity score [42, 44]. In the present analyses, the severity score assumes the values 0, 1, or 2, indicating the number of unfavourable predictors (when three predictors were unfavourable, as occurred in a few patients, this was counted as a score of 2). The severity score was considered to be a quantitative covariate.

Second, we created two different Cox models for reaching endpoints. One ("early") was for the first part of the follow-up, censored at a selected duration. The chosen censoring point, or cut-off time, was different for different endpoints, amounting to 15 years for progression, 25 years for EDSS6, 30 years for EDSS7, and 35 years for EDSS10var. These selected cut-off times were close to the

average times to the respective endpoints or censoring in the RR-SP subset. The second ("late") model was constructed using only the observations that reached an endpoint or were censored after the cut-off time. Consequently, the model described time from the cut-off time to endpoint, not time from onset (although the predictors used were descriptors of the onset attack).

The difference between these two Cox models was further illustrated by K–M estimates of time to endpoints for different severity scores, first from onset throughout the 50-year follow-up, then from the defined cut-off times.

Third, a separate analysis was performed for each gender. These models included only two independent variables: age at onset and the severity score. No interaction between these two variables was included for any endpoint.

Results

Time to disability milestones

In the RR-SP subset ($n = 212$, Fig. 1), the median time to a second event was 2 years, to SP 12 years, to EDSS6 22 years, and to EDSS7 36 years. Fifty years after onset, survival analysis showed that 14 % of patients remained non-progressive, 22 % were progressive but ambulatory, 16 % were disabled (non-ambulatory), and 48 % had died from MS (including 12 % with combined cause of death). A similar survival analysis in the RR-SP-CIS subset ($n = 254$, Fig. 2) found a median time of 2 years to the second event (not expected to occur in all patients in this subset), 15 years to SP, 26 years to EDSS6, and 48 years to

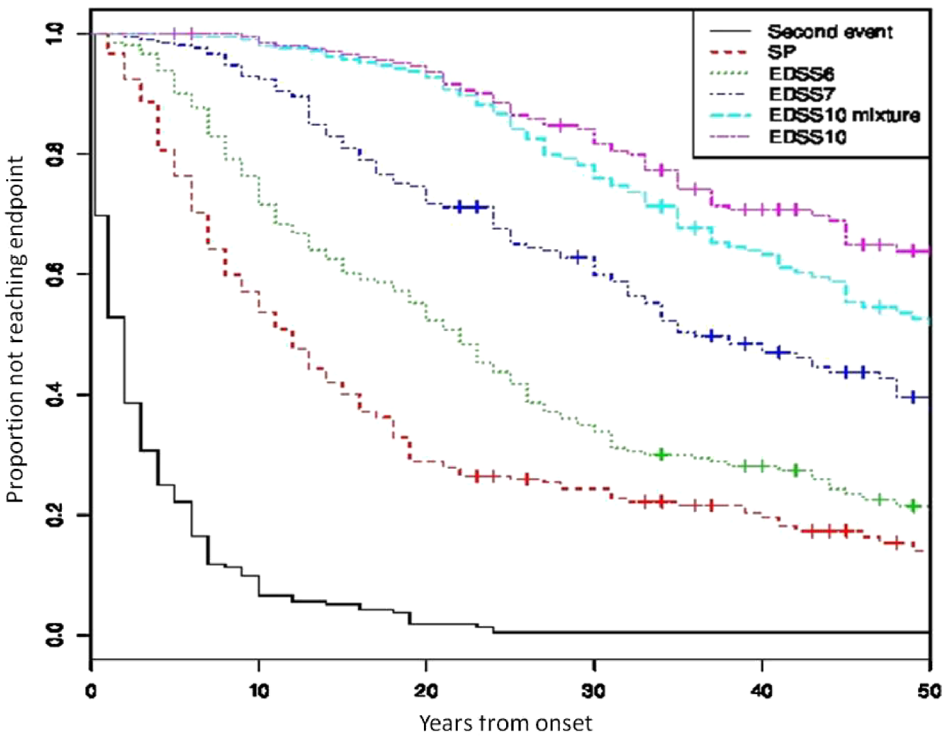

Fig. 1 50-year Kaplan–Meier estimates of time from onset to second event, onset of secondary progression, EDSS6, EDSS7, EDSS10var, and EDSS10 for subset RR-SP ($n = 212$). The matrix shows the number at risk for each endpoint per decade. Censoring is indicated by crosses, though censoring is sometimes concealed in steps indicating events. One patient at risk of a second event (year 30–50) had two attacks of myelopathy within 5 years and was not monophasic (not "CIS only"). However, due to stringent criteria (two CNS regions involved with evidence for one), this patient did not qualify for CPMS

Year	0	10	20	30	40	50
2nd event	212	21	4	1	1	1
SPMS	212	121	59	45	29	8
EDSS6	212	161	112	64	41	14
EDSS7	212	196	149	109	68	32
EDSS10	212	208	187	139	94	47

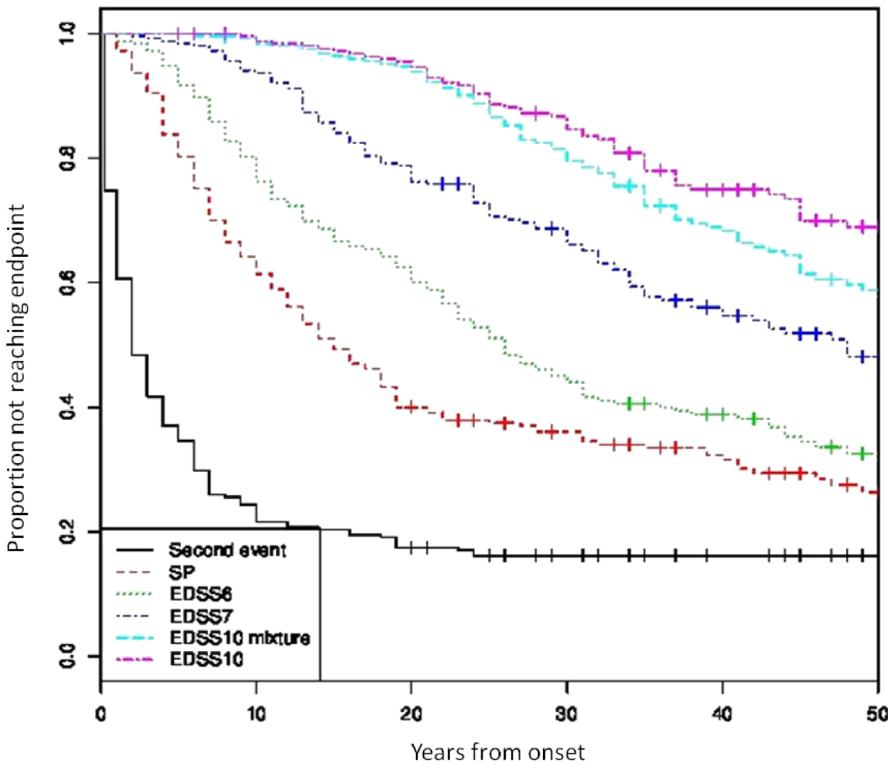

Fig. 2 50-year Kaplan–Meier estimates of time from onset to second event, onset of secondary progression, EDSS6, EDSS7, EDSS10var. and EDSS10 for subset RR-SP-CIS ($n = 254$). The matrix shows number at risk for each endpoint per decade. Censoring indicated by crosses, although most censoring is concealed in steps indicating events

Year	0	10	20	30	40	50
2nd event	254	61	42	28	20	10
SPMS	254	162	97	72	48	17
EDSS6	254	202	151	91	60	23
EDSS7	254	237	188	136	87	41
EDSS10	254	249	226	166	113	56

EDSS7. Fifty years after onset, survival analysis showed that 25 % of patients remained non-progressive, 20 % were progressive while remaining ambulatory, 13 % were disabled, and 31 % had died from MS (EDSS10, 42 % EDSS10var). With primary progression, all ($n = 44$, Fig. S1) patients reached EDSS6: one remained EDSS6 and one remained EDSS7, both surviving 50 years of disease.

Ninety-two patients died from MS (EDSS10). Competing causes of death (from MS and other potentially lethal diseases) were noted in 29 patients. Sixty-seven patients who died from other diseases were censored during the study period (Table 1).

A long interval (>1 year) between the last examination and death occurred in 27 patients (mean 5.9 years). Four patients moved abroad: one was examined in Denmark by our team and three had extended unmonitored intervals (time from last examination to death: 10 years, 27 years, or unknown). Four patients refused follow-up an average 16 years before death or study termination.

Age at disability milestones

Patients' ages when they reached the defined disability endpoints were estimated using the data from the RR-SP subset (Fig. 3). The proportion of patients estimated to remain non-progressive at 60 years of age in the K–M analysis applied from birth (estimate **b**, $n = 212$) was 25 %, (maximum 26 % using estimate **a**, and minimum 23 % using estimate **c**). The estimate for 80 years was 16 % (maximum 18 % and minimum 5 %).

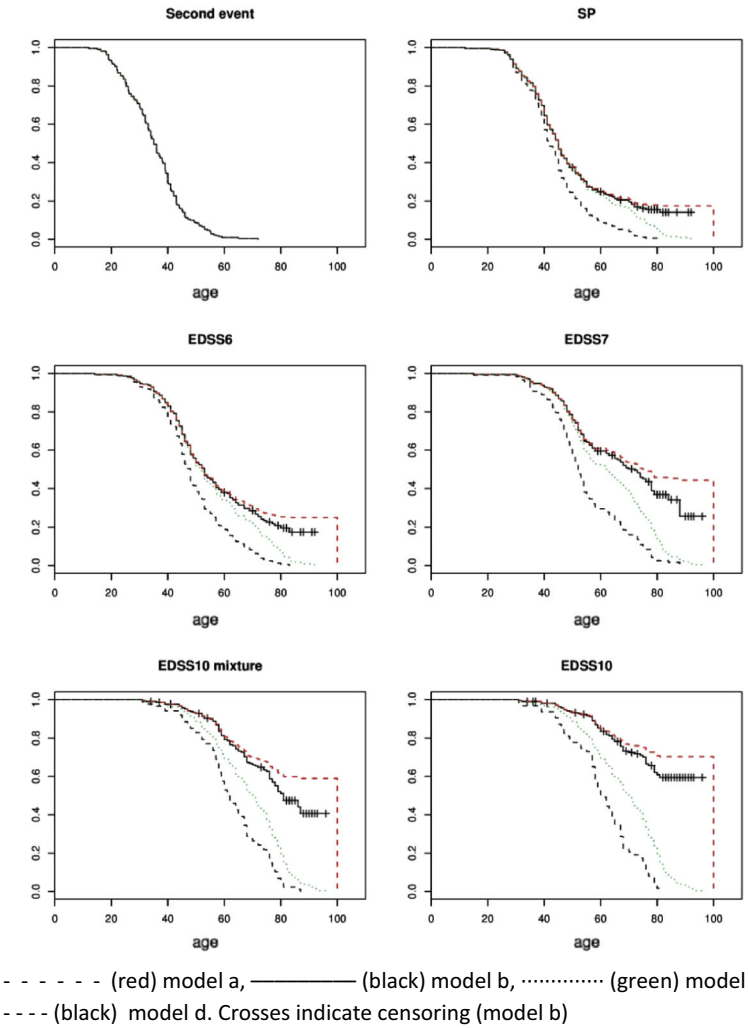

Fig. 3 Four estimates (or models) of age at disability endpoints in subset RR-SP ($n = 212$). Censoring is indicated by crosses. Estimate **a** indicates maximum time with a hypothetical very late time for outcome in censored cases. Estimate **b** is a Kaplan–Meier estimate from birth. Estimate **c** is the minimum time assuming that the endpoint occurred immediately after censoring. Estimate **d** is a distribution estimate including only cases reaching the endpoint

The proportion estimated to have reached EDSS6 increased from approximately 20 years of age, reaching 50 % at 47 years of age and 83 % at 80 years of age. For age at subsequent disability milestones (EDSS7) and death from MS (EDSS10), the K–M estimate applied from birth showed a similar pattern (Fig. 3). Advanced age was dominated by an increase in censoring and decreasing numbers at risk. However, no age seemed safe in terms of the risk of further MS-related disability.

For the sake of comparisons with previous large natural history studies [11], we calculated an additional age distribution estimate without censoring (**d**) including only patients who reached the endpoint in this analysis ($n = 176$). The proportions reaching endpoints were smaller than in the minimum estimate (**c**).

Univariate analyses

Using the RR-SP subset, the predictors onset age, monofocal symptoms and complete remission of the onset attack were significant for time to SP (Table 2). Using the RR-SP-CIS subset, afferent lesion and complete remission were predictive of SPMS ($p = 0.001$ and 0.001) and EDSS 7 ($p = 0.006$ and 0.043), whereas only complete remission remained significant for EDSS10 ($p = 0.021$; Table 3; Fig. 4). We found that age at onset was associated with the risk of SP. Patients with lower age at onset had longer time to SP.

Patients in the RR-SP and RR-SP-CIS subset with low severity scores had longer times to the endpoints SP, EDSS7, and EDSS10 (Fig. 5a). Thus, no additional predictive information was obtained from the severity score after the cut-off point; the separation of the K–M graphs observed at the cut-off point (approximately 15 years for SP) was sustained during the remaining follow-up (Fig. 5b).

Multivariate analysis

Our argument for separate gender analyses was the presence of many interactions involving gender when Cox

Table 2 Kaplan–Meier estimates of time to endpoints in subset RR-SP ($n = 212$)

Factor	n	Median time to SPMS		Median time to EDSS7		Median time to EDSS10	
		Years (95 % CI)	p value	Years (95 % CI)	p value	Years (95 % CI)	p value
Overall	212	12 (10–14)		36 (32–48)		60 (55–NA^2)	
Gender							
Female	137	13 (11–16)	0.125	43 (34–50)	0.172	60 (58–NA^2)	0.174
Male	75	10 (6–15)		31 (25–54)		55 (48–NA^2)	
Onset age							
<30 years	87	16 (13–19)	0.03	40 (33–51)	0.209	58 (55–NA^2)	0.698
≥30 years	125	8 (7–12)		35 (30–48)		NA^1 (NA^2–NA^2)	
Symptoms							
Afferent	68	14 (10–19)	0.198	48 (34–NA^2)	0.131	58 (54–NA^2)	0.381
Efferent	144	11 (8–13)		33 (28–47)		60 (55–NA^2)	
Complete	120	14 (12–18)	0.012	43 (34–51)	0.185	60 (55–NA^2)	0.061
Incomplete remission	92	8 (6–12)		34 (30–47)		NA^1 (45–NA^2)	
Monofocal[a]	197	12 (10–15)	0.03	40 (33–48)	0.004	60 (55–NA^2)	0.039
Polyfocal	15	7 (4–18)		16 (13–NA^2)		45 (24–NA^2)	

CI confidence interval, NA^1 survival function estimates that less than 50 % of patients at risk reach endpoint, NA^2 CI out of range. Mean time to EDSS10 for <30 years of onset was 50.8 years and for >30 years of 47.5 years. Mean time to EDSS10 for remission 51.9 and incomplete remission 46.5 years

[a] Strictly: not polyfocal; definition in text

Table 3 Kaplan–Meier estimates of time to endpoints in subset RR-SP-CIS ($n = 254$)

Factor	n	Median time to SPMS		Median time to EDSS7		Median time to EDSS10	
		Years (95 % CI)	p value	Years (95 % CI)	p value	Years (95 % CI)	p value
Overall	254	15 (13–18)		48 (38–52)		60 (58–NA^2)	
Gender							
Female	165	16 (13–21)	0.136	50 (43–NA^2)	0.146	60 (58–NA^2)	0.154
Male	89	13 (9–18)		35 (30–NA^2)		55 (54–NA^2)	
Onset age							
<30 years	106	19 (15–28)	0.060	50 (38–NA^2)	0.153	60 (55–NA^2)	0.576
≥30 years	148	11 (8–16)		43 (34–NA^2)		NA^1 (NA^2–NA^2)	
Onset							
Afferent	94	22 (16–51)	0.001	51 (48–NA^2)	0.006	58 (58–NA^2)	0.103
Efferent	160	12 (10–16)		40 (31–50)		60 (55–NA^2)	
Complete	151	18 (15–32)	0.001	50 (43–NA^2)	0.043	60 (58–NA^2)	0.021
Incomplete remission	103	10 (7–16)		34 (32–NA^2)		NA^1 (45–NA^2)	
Monofocal[a]	234	16 (13–19)	0.484	48 (40–54)	0.086	60 (58–NA^2)	0.155
Polyfocal	20	11 (5–NA^2)		34 (16–NA^2)		NA^1 (30–NA^2)	

CI Confidence interval, NA^1 survival function estimates that less than 50 % of patients at risk reach endpoint, NA^2 CI out of range. Mean time to EDSS10 for onset <30 years of age was 52.5 years and for onset >30 years of age was 48.9 years. Mean time to EDSS10 complete remission was 53.5 years and for incomplete remission 47.8 years. Mean time to EDSS10 for onset <30 years of age was 52.0 years and for onset >30 years of age was 41.3 years

[a] Strictly: not polyfocal; definition in text

models were based on the whole data set. Here, we illustrate one of these interactions, namely the interaction between age of onset and gender. K–M estimates were calculated in sub-populations defined by gender and age at onset (<25 and ≥25 years of age). This analysis revealed that the effect of onset age on time to SP differed between males and females (Fig. 6). The directions of the effect were opposite in the two age groups; for younger patients,

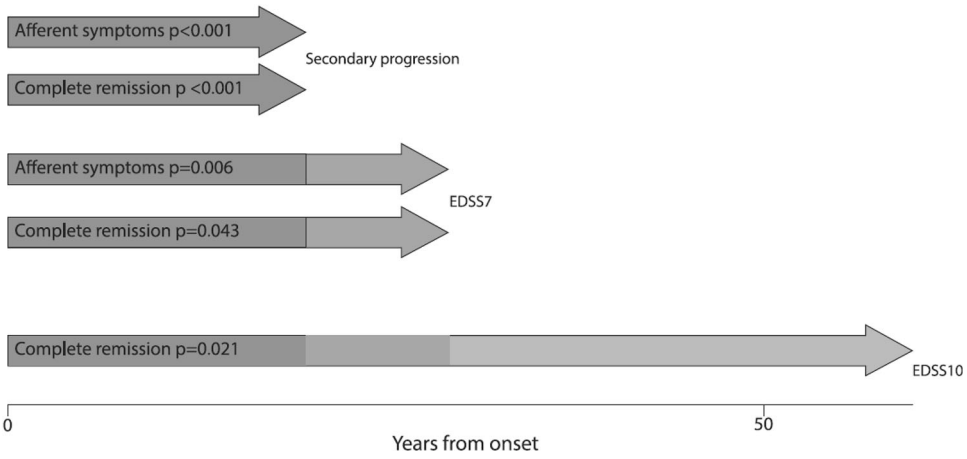

Fig. 4 Summary of Kaplan–Meier analyses of time to SP, EDSS7, and EDSS10 ($n = 254$). Results are from a log-rank test of predictors from onset

the survival rate was higher for males, whereas for older patients, the survival rate was higher for females. Differences between the age groups were observed mainly among men.

A single Cox model was not appropriate for modelling the entire data set. In the RR-SP-CIS subset ($n = 254$), we considered predictions from onset data to the cut-off points and from the cut-off point to the end of follow-up (Table 4a, b). The factor "age at onset" was significant for risk of SP in men ($p = 0.043$), but not in women. The hazard ratios (HRs) increased approximately 5 % per year for men and only 0.05 % for women. On the other hand, the effect associated with severity score was significant for both genders, with a moderately larger HR estimate for women (HR 1.77 per step in the score, $p = 0.00078$ for women and HR 1.53, $p = 0.034$ for men). We observed a similar pattern for EDSS6 among men and women. The risk estimate of reaching EDSS7 increased with a higher severity score (HR = 2.03 per step in the score, $p = 0.0018$) in women but not in men. As there were fewer men than women, estimates of a similar magnitude may be significant for women but not for men. However, the general pattern of estimated HRs remained the same for both genders, with the severity score being clearly predictive in women. The severity score was significantly predictive of EDSS10var only in women (HR 2.31 per step, $p = 0.0022$). In men, age at onset remained a significant predictor of EDSS10 ($p = 0.014$).

Considering predictions of the course after the cut-off points (Table 4a, b), few effects of onset predictors were observed. The estimated HR for age at onset was even <1 for a single endpoint in men, namely SP ($p = 0.024$), indicating that time to this particular endpoint did increase with onset age. However, for the severity score, the HR estimate was consistently >1 in men and significant for EDSS7 ($p = 0.032$). No significantly predictive patterns were found for women.

Restricting the analysis to the RR-SP subset and considering predictions from onset data and follow-up from onset until the cut-off point, the pattern of HR in men and women was consistent with the conclusions from the RR-SP-CIS subset. Considering predictions of the course after the cut-off points, the general conclusion was still that no additional predictive power was added.

Rate of SP

In order to assess the rate of progression from onset of SP, we studied time from SP to EDSS7. This interval was not influenced by predictors recorded at onset. However, we observed that a shorter time from onset to SP was associated with a shorter time from SP to EDSS7 in women only ($p = 0.03$).

Final follow-up

The final follow-up of "CIS only" and non-progressive patients was reported previously [32, 41]. The final follow-up of SP patients alive 2009–2012 ($n = 22$) is summarized in Supplementary Table S2. The median EDSS was 6.5–7.0 (range 2.0–9.0).

Discussion

We recently reported the 50-year outcomes for monophasic ("CIS only") and non-progressive patients from this cohort [32, 41] using the first 12 years of follow-up as historical control data [44]. Here, we present the 50-year outcomes for the whole cohort, focusing on those with attack onset. After an initial MS attack in 254 patients, K–M estimates of time to different endpoints showed a final three-way split, as slightly less than one-third of patients remained non-progressive (including monophasic "CIS only"

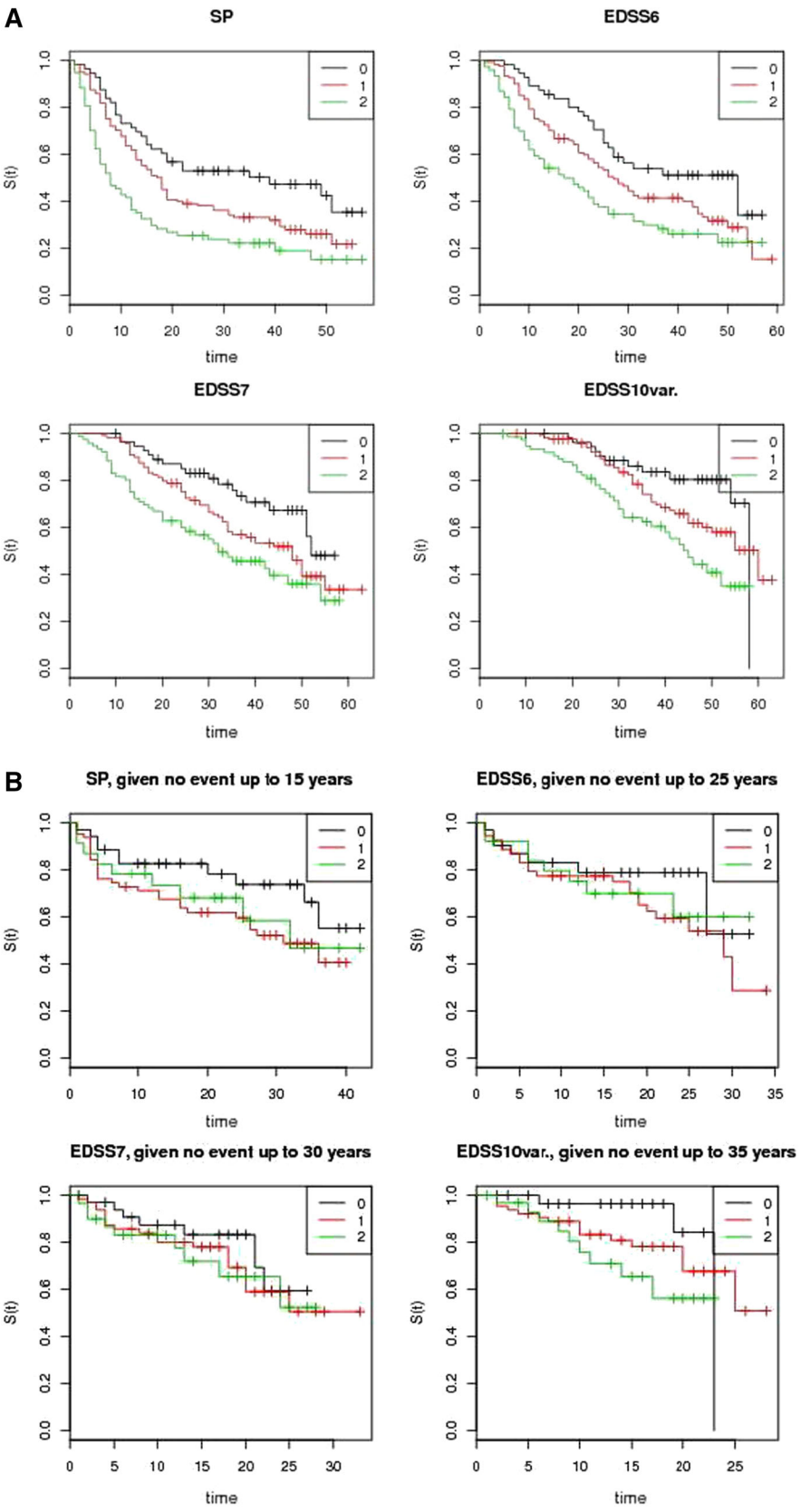

Fig. 5 Kaplan–Meier estimate of time to the endpoints SP, EDSS6, EDSS 7, and EDSS10 stratified according to severity score (0 = no, 1 = one, and 2 = two or three unfavourable characteristics in the onset attack) in subset RR-SP-CIS ($n = 254$). Multivariate Cox analysis confirmed prediction from onset to the cut-off point, whereas the range of the Kaplan–Meier analysis **a** included disability milestones during five decades. **b** Included only the patients with time to event or censoring greater than the cut-off time, which is indicated on the figures. Time to event was left truncated at the cut-off point, which is close to the mean time to outcome (or censoring). Comparing **a** and **b** shows that the severity score at onset provides little or no further information after the cut-off point

patients), one-third were progressive (the majority ambulatory), and slightly more than one-third had died from MS after 50 years of follow-up. However, no age seemed safe in terms of the risk of further MS-related disability, arguing against a previous report suggesting that the risk of progression levelled out approximately 35 years after onset [39].

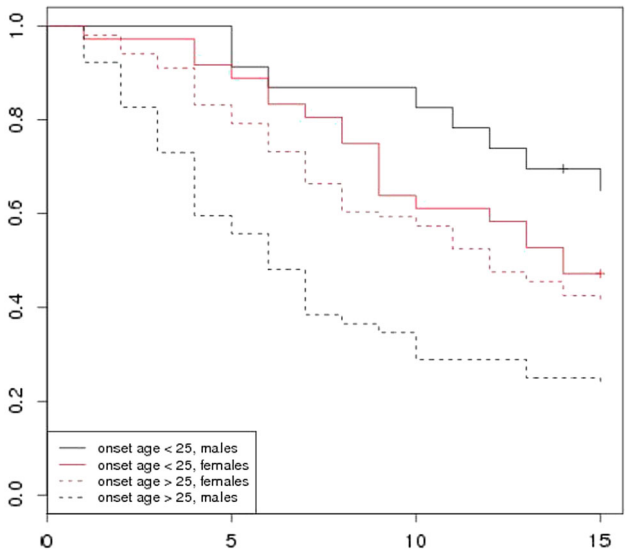

Fig. 6 Kaplan–Meier estimates of time to SP stratified by gender and onset age (younger and older than 25 years of age), illustrating the interaction between these two predictors

A cluster of predictors associated with the onset attack, with the favourable parameters being complete remission, afferent symptoms, and monofocal symptomatology, was combined into one severity score, an expression of the severity of the very first stage of the disease, which was then used as a predictor in the survival analysis [37]. This score was significantly predictive (HR estimates in the magnitude of 2 for each step of the severity score) of SP and all subsequent disability endpoints during the 50-year follow-up in women and of SP and EDSS6 in men. In men, we found a strong association between age at onset and disability outcomes, which attenuated the predictive power of the onset severity score for the times to distant outcomes. Moreover, in patients reaching their disability endpoint after certain cut-off points (e.g., 15 years for SP and 25 years for EDSS6), the onset characteristics did not contribute any additional predictive information. The dependency of the disability endpoints on the onset predictors may be explained by the effect that these predictors have on SP. Thus, the relationship to the following endpoints probably relates to the fact that the continuous disability accrual in SP is independent ("amnesic") of the previous course [12, 15]. Admittedly, a previous GIC study

Table 4 Multivariate Cox regression analysis of time to different endpoints by potential risk factors in subset RR-SP-CIS ($n = 254$)

a. Men ($n = 89$)

Incidence	Factor	SP HR	p value	EDSS6 HR	p value	EDSS7 HR	p value	EDSS10var HR	p value
Early[a]	Severity score (per step)[c]	1.534 ($n = 89$)	0.0336	1.494 ($n = 89$)	0.0459	1.364 ($n = 89$)	0.186	0.995 ($n = 89$)	0.984
	Age at onset	1.049	0.00426	1.052	0.0048	1.033	0.100	1.061	0.0135
Late[b]	Severity score (per step)[c]	1.814 ($n = 38$)	0.106	2.140 ($n = 36$)	0.117	3.295 ($n = 39$)	0.0321	1.905 ($n = 38$)	0.232
	Age at onset	0.925	0.0242	0.935	0.108	0.972	0.506	0.983	0.727

b. Women ($n = 165$)

Incidence	Factor	SP HR	p value	EDSS6 HR	p value	EDDS7 HR	p value	EDSS10var HR	p value
Early[a]	Severity score (0–2)[c]	1.768 ($n = 165$)	0.000779	1.621 ($n = 165$)	0.00468	2.029 ($n = 165$)	0.0018	2.314 ($n = 165$)	0.00220
	Age at onset	1.0059	0.568	1.00684	0.540	0.989	0.4549	1.0123	0.486
Late[b]	Severity score (0–2)[c]	1.126 ($n = 84$)	0.651	0.996 ($n = 77$)	0.990	0.955 ($n = 92$)	0.868	1.840 ($n = 94$)	0.102
	Age at onset	0.966	0.108	0.955	0.108	0.978	0.425	1.00223	0.948

HR hazard ratio per step (0–2) in the severity score

[a] The corresponding model was created using the whole data set, but with outcomes later than a certain cut-off point set to be censored at this point

[b] The corresponding model was created using only patients who did not reach outcome before the cut-off time

[c] The severity score describes the onset attack as measured by three onset symptoms

suggested an exception from this independent state of the SP; a short duration from onset to SP was predictive of a high progression rate [15]. This finding was confirmed (for time to EDSS7 in women) in the present study, although the slope of SP was not affected by the duration of the RR phase in another study [39]. However, if we accept the relationship between RR phase duration and SP rate, this would also tend to synchronize the time to SP and the next endpoints. Thus, the prediction of time to onset of SP influences the time to the subsequent disability milestones.

The GIC

The main asset of the present 50-year follow-up study is the prediction of disease course over decades from an incidence cohort, a design originating from the seminal epidemiological studies of Olmsted County in the US. Longitudinal follow-up of an incidence cohort provides data from a representative sample of a patient population, reducing inclusion bias [23, 34]. The primary catchment area for the Neurology Department at Sahlgrenska University Hospital and the Gothenburg epidemiological (prevalence and incidence) area for the GIC were identical, and apart from one private practice from which records were available for the MS team, there were no other neurology services in this area until 1977. A single archive collected records from all neurological wards, the out-patient department, and the consultations. Neurology was not established as a speciality in Gothenburg until the late 1940s, and there was a strong tradition among Gothenburg general practitioners to refer all patients with suspected neurological symptoms to the Sahlgrenska neurology clinic (personal communication from professor Tore Broman). A full-time team, including a research secretary, was dedicated to ascertaining cases belonging to the 1950–1964 incidence cohort. This effort continued during the incidence period and the following decades [7]. An ophthalmologist referred patients with optic neuritis to the study team. A first transversal examination by the team was performed in 1965–1970 (by Broman, Bergmann, and Andersen). Despite these efforts, we cannot claim that we have retrieved all individuals belonging to the GIC according to our definition. Problems in this regard are apparent from the changes in the patient population since the 1950–1964 incidence period.

Without adherence to a prospective geographic temporal definition and a focused effort to ascertain incident cases, there is a risk of bias from convenience sampling [33]. Recruiting patients from MS rehabilitation clinics may result in missing extreme variants, benign or lethal cases [4]. The detailed GIC information on each relapse facilitates evaluation of the degree of disease activity from onset. This is a precondition for studying the influences of genetic [37] and environmental factors on disease course. However, data on smoking, body mass index, and vitamin D status, which are more relevant for the pre-symptomatic stages, are not available for the GIC. Socioeconomic data were not evaluated. We are not aware of any study addressing this factor in Sweden in relation to MS. However, a study using the national MS register in Denmark, a Scandinavian country with similar sociomedical structure, found that socio-economic factors did not influence the risk of MS [27].

Patient subsets

Prediction from CIS is difficult for data defined by MS diagnosis according to Poser, as this violates the preconditions for survival analysis by embedding outcome data in the predictors. The estimated survival time to outcome tends to be too short. The classical natural history studies are generally subject to this limitation [13, 35, 51]. We used a more accurate K–M analysis that includes data from both patients ($n = 254$) considered "CIS only" ($n = 42$) and those with RRMS (MS diagnosis according to Poser, $n = 212$), accepting "CIS only" as one of the long-term outcomes [15]. Including CIS is reasonable considering that the contemporary patient population is mainly MR-defined, and 50–70 % of patients with CIS have asymptomatic MRI findings [29].

Censoring

A crucial prerequisite for survival analysis is that censoring is neutral, indicating an absence of a relationship between the disease under study and the cause of censoring. This may be objectionable when censoring occurs as a consequence of related diseases. In a study based on the Danish MS and cancer registries, the overall risk for cancer was reduced 16 % in men with MS due to reduced numbers of cancers of the digestive, respiratory, and genital organs. In women with MS, the overall risk of cancer was not significantly altered, but a 21 % increase in the risk of breast cancer was reported [31]. A large population-based study in New York City reported a decreased risk [odds ratio (OR) 0.58] of ischemic heart disease and myocardial infarction (OR 0.78) but increased risk (OR 1.66) of ischemic stroke in MS patients [1]. A study matching the Danish MS registry and the National Registry of Patients over a 30-year follow-up confirmed an excess risk of ischemic stroke (IRR 1.23) [10]. Cerebral hypoperfusion occurs in MS and may be secondary to MS pathology [14]. Thus, deviations from the neutrality of censoring seem to be moderate. Furthermore, the GIC database contains detailed records on comorbidities, which allows for adequate individual censoring.

Changes in the patient population and mortality since the incidence period

In recent epidemiological studies in Sweden, the incidence of MS has been higher (6.4/100,000/year) [6] than previously reported from the Gothenburg area (5.3/100,000/year) [7]. Several contemporary investigations found that the disease course is becoming milder [19, 20, 28].

An analogous caveat regards the diminishing mortality due to MS, which is likely to have markedly reduced the proportion of patients reaching EDSS10 today. A study from the Danish MS registry reported that total mortality (MS and non-MS) has diminished significantly over successive decades [8], probably due to progress in several health care sectors. We have not been able to find reports on coincident trends in MS-specific mortality. In the most severe category, >EDSS7, we have seen the most critical advances in MS health care. However, neurorehabilitation could improve motor, cognitive, and other performance levels without changing the EDSS level [38]. Therefore, we contend that the relationships we report between the disability categories up to EDSS7 are not invalidated by these fundamental health care changes.

Time from onset to disability milestones

The proportion of extreme final outcomes observed in this incidence cohort, benign or lethal, was conspicuously larger than in older natural history studies based on the large London, Ontario, cohort [52]. Definitions of SP may vary [46], and the relatively short duration until conversion to SP contrasting with a relatively long delay to EDSS6 in the GIC suggests that the GIC criteria for SP are more sensitive. The median time from onset to EDSS6 in the present study was 22 to 26 years (for our two subgroups), which is intermediate between the time reported based on the updated London, Ontario, database (18 years) [40] and the time (28 years) recently presented in a cohort stated to have a slower progression than previously reported [45].

After 50 years, 14 to 26 % of the GIC remained non-progressive. Indicating a surprisingly benign prognosis, it was recently reported from the London, Ontario database that the rate of conversion to SP levelled out 15 years after onset, to a tapering "final total" of 66 % after 50 years, based on K–M analysis (Fig. 3) [39]. A similar favourable prognosis was obtained from data showing that 45 % of the patients had not reached progression 35 years after onset (model 2) [50]. Recent data include a larger proportion of patients treated by disease-modifying drugs, and the latter data differs from the previous cohorts by using the McDonald criteria, which encompass a more benign proportion of the MS population.

Age and MS course

MS has been proposed to be an age-dependent disease [12]. This statement seems to have a double meaning: lower age at onset is a predictor of longer time to disability, and the risk of reaching disability milestones is associated with age, partially counteracting the effect of age at onset [39]. Studies of the age at transition to SP have not identified any clinical onset predictors beyond gender and age at onset per se [12, 46] or in combination with motor symptoms [21]. There is evidence that the rate of SP or the course after EDSS4 is independent of the individual antecedent clinical course [15, 53], with the exception that the interval between onset of MS to SP was predictive of the progression rate using a sensitive scoring system [15].

The data on age at onset of disability are disparate based on different models. The median age at transition to SP has been reported to be between 50 and 60 years of age using K–M analysis with censoring (Fig. 1) [21], or 38 years with a distribution estimate without censoring [12]. At least two reports on age-related disability have presented outcomes with or without censoring. At 75 years of age, 98 % of cases had reached SP, 62 % when including the censored cases [50]. Another study focusing on differences between SPMS and PPMS showed that the median age at transition to SP decreased with increasing follow-up in the RRMS phase. Using "complete" (standard) K–M analysis the median age was 49 years, but it was 43 years when their "incomplete" K–M analysis (corresponding to our distribution estimate without censoring) was used. The "incomplete" method resulted in an underestimation of the time to SP [46]. This distribution estimate is an unreliable method for assessing the median time to SP because it is strongly confounded by the length of follow-up. In our study, the median age at SP was approximately 42 years using a distribution estimate without censoring and 45 years with a K–M estimate. However, the difference between these two estimates was more dramatic for age at later disability milestones. Eighty-four percent of the GIC cohort had reached SP at 75 years of age according to the K–M estimate. Our findings of age at disability milestones were within the range of results in previous studies.

Gender

Women have often been described as having a more favourable MS prognosis than men. However, a stratified study [35] revealed that this difference in outcome is mainly due to a higher proportion of males with a primary progressive course. In contrast, no significant gender differences were found among RRMS onset patients. In a study from MSbase, women had a higher frequency of relapse than men [16]. There was a surplus of women

among those with longest time to SP [48]. In the present study, gender was not an independent predictor of long-term disability in a univariate analysis, but it did have an impact via an important interaction. We found that age at onset did not generally influence the outcome in women, but it did influence the outcome in men. Thus, younger men had a better prognosis than women of a similar age in regard to SP risk, whereas men who were older at onset clearly had a worse outcome. The biological background for this negative age-related trend in men remains to be clarified.

Prediction range

A temporal limitation was reported in the British Columbia cohort; relapse frequency was associated with the hazard of disease progression during the first 5-year period. However, this short- or medium-term predictive association diminished during the following 5-year period and was essentially lost thereafter [47]. We here found that age at onset and the severity score were significant predictors of the transition to SP for approximately half the range to the disability endpoints, and the prediction of SP was transmitted to the subsequent disability milestones within the 50-year follow-up. A multi-step mechanism may be involved in the long-term prediction from onset, as the degree of severity of the first attack is mirrored in subsequent attacks [5].

Conclusions

In conclusion, the additional contributions from the present cohort, the GIC, to several other qualified natural history studies are: (a) a truly observational and mainly prospective onset of the whole cohort, markedly reducing inclusion bias; (b) probably the longest untreated longitudinal observation from an incidence basis observed by a research team; (c) a detailed database with information on each attack allowing for long-term prediction from onset age and clinical characteristics, disproving claims that such prediction is impossible.

Our life-long outcome data for MS reveal a higher proportion of extreme outcomes (benign and lethal) than older natural history studies, although generally with a more favourable prognosis, approaching data from more recent studies. However, other cohorts established recently, after the general use of MRI and the accessibility of effective interventions show a still more favourable course. Our findings concerning age at disability milestones were intermediate between results from previous studies. We used distribution estimates with censoring, avoiding confounding by the length of follow-up.

The statement that age at onset is a predictor of disability milestones was supported by our results for men, but not for women. Moreover, a severity score constructed from a cluster of previously reported predictors of onset provided a consistent prediction of times to SP and disability endpoints during the 50-year follow-up. The predictors retrieved in the present study had a HR estimate in the magnitude of 2 per score step, which is clinically meaningful. This applies primarily to prediction of SP which was, however, passively transmitted to the subsequent disability endpoints, and no additional predictive information from onset was added after 15–30 years of follow-up.

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References

1. Allen NB, Lichtman JH, Cohen HW, Fang J, Brass LM, Alderman MH (2008) Vascular disease among hospitalized multiple sclerosis patients. Neuroepidemiology 30:234–238
2. Amato MP, Ponziani G (2000) A prospective study on the prognosis of multiple sclerosis. Neurol Sci 21:S831–S838
3. Andersen O (2012) From the Gothenburg cohort to the Swedish multiple sclerosis registry. Acta Neurol Scand Suppl:13-19
4. Andersen O (2008) Natural history of multiple sclerosis. In: Raine C, McFarland HF, Hohlfeld R (eds) Multiple Sclerosis: a comprehensive text. Saunders Elsevier, Edinburgh, pp 100–120
5. Andersen O (1980) Restricted dissemination of clinically defined attacks in an MS incidence material. Acta Neurol Scand Suppl 77:1–70
6. Bostrom I, Callander M, Kurtzke JF, Landtblom AM (2009) High prevalence of multiple sclerosis in the Swedish county of Varmland. Mult Scler 15:1253–1262

7. Broman T, Andersen O, Bergmann L (1981) Clinical studies on multiple sclerosis. I. Presentation of an incidence material from Gothenburg. Acta Neurol Scand 63:6–33
8. Bronnum-Hansen H, Koch-Henriksen N, Hyllested K (1994) Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey. Neurology 44:1901–1907
9. Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, Vrethem M, Fredrikson S, Martin C, Sandstedt A, Uggla B, Lenhoff S, Johansson JE, Isaksson C, Hagglund H, Carlson K, Fagius J (2014) Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. J Neurol Neurosurg Psychiatry 85:1116–1121
10. Christiansen CF, Christensen S, Farkas DK, Miret M, Sorensen HT, Pedersen L (2010) Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology 35:267–274
11. Confavreux C, Vukusic S (2006) Age at disability milestones in multiple sclerosis. Brain 129:595–605
12. Confavreux C, Vukusic S (2006) Natural history of multiple sclerosis: a unifying concept. Brain 129:606–616
13. Confavreux C, Vukusic S, Adeleine P (2003) Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 126:770–782
14. D'Haeseleer M, Cambron M, Vanopdenbosch L, De Keyser J (2011) Vascular aspects of multiple sclerosis. Lancet Neurol 10:657–666
15. Eriksson M, Andersen O, Runmarker B (2003) Long-term follow up of patients with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis. Mult Scler 9:260–274
16. Kalincik T, Vivek V, Jokubaitis V, Lechner-Scott J, Trojano M, Izquierdo G, Lugaresi A, Grand'maison F, Hupperts R, Oreja-Guevara C, Bergamaschi R, Iuliano G, Alroughani R, Van Pesch V, Amato MP, Slee M, Verheul F, Fernandez-Bolanos R, Fiol M, Spitaleri DL, Cristiano E, Gray O, Cabrera-Gomez JA, Shaygannejad V, Herbert J, Vucic S, Needham M, Petkovska-Boskova T, Sirbu CA, Duquette P, Girard M, Grammond P, Boz C, Giuliani G, Rio ME, Barnett M, Flechter S, Moore F, Singhal B, Bacile EA, Saladino ML, Shaw C, Skromne E, Poehlau D, Vella N, Spelman T, Liew D, Kilpatrick TJ, Butzkueven H (2013) Sex as a determinant of relapse incidence and progressive course of multiple sclerosis. Brain 136:3609–3617
17. Kantarci O, Siva A, Eraksoy M, Karabudak R, Sutlas N, Agaoglu J, Turan F, Ozmenoglu M, Togrul E, Demirkiran M (1998) Survival and predictors of disability in Turkish MS patients. Turkish Multiple Sclerosis Study Group (TUMSSG). Neurology 51:765–772
18. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, Herbert J (2013) Natural history of multiple sclerosis symptoms. Int J MS Care 15:146–158
19. Kister I, Chamot E, Bacon JH, Cutter G, Herbert J (2011) Trend for decreasing multiple sclerosis severity scores (MSSS) with increasing calendar year of enrollment into the New York State Multiple Sclerosis Consortium. Mult Scler 17:725–733
20. Kister I, Chamot E, Cutter G, Bacon TE, Jokubaitis VG, Hughes SE, Gray OM, Trojano M, Izquierdo G, Grand'Maison F, Duquette P, Lugaresi A, Grammond P, Boz C, Hupperts R, Petersen T, Giuliani G, Oreja-Guevara C, Iuliano G, Lechner-Scott J, Bergamaschi R, Rio ME, Verheul F, Fiol M, Van Pesch V, Slee M, Butzkueven H, Herbert J (2012) Increasing age at disability milestones among MS patients in the MSBase Registry. J Neurol Sci 318:94–99
21. Koch M, Kingwell E, Rieckmann P, Tremlett H (2010) The natural history of secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 81:1039–1043
22. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC (2006) The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. Brain 129:584–594
23. Kurland LT (1994) The evolution of multiple sclerosis epidemiology. Ann Neurol 36(Suppl):S2–S5
24. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452
25. Levic ZM, Dujmovic I, Pekmezovic T, Jarebinski M, Marinkovic J, Stojsavljevic N, Drulovic J (1999) Prognostic factors for survival in multiple sclerosis. Mult Scler 5:171–178
26. Lublin FD, Reingold SC (1996) Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 46:907–911
27. Magyari M, Koch-Henriksen N, Pfleger CC, Soelberg Sörensen P (2014) Physical and social environment and the risk of multiple sclerosis. Multiple sclerosis and related disorders 3:600–606
28. Marrie RA, Cutter G, Tyry T, Hadjimichael O, Campagnolo D, Vollmer T (2005) Changes in the ascertainment of multiple sclerosis. Neurology 65:1066–1070
29. Miller DH, Chard DT, Ciccarelli O (2012) Clinically isolated syndromes. Lancet Neurol 11:157–169
30. Muller R (1951) Course and prognosis of disseminated sclerosis in relation to age of onset. AMA Arch Neurol Psychiatry 66:561–570
31. Nielsen NM, Rostgaard K, Rasmussen S, Koch-Henriksen N, Storm HH, Melbye M, Hjalgrim H (2006) Cancer risk among patients with multiple sclerosis: a population-based register study. Int J Cancer 118:979–984
32. Novakova L, Skoog B, Runmarker B, Ekholm S, Winblad S, Lisovskaja V, Andersen O (2013) Clinically isolated syndromes with no further disease activity suggestive of multiple sclerosis at the age of population life expectancy. Mult Scler J 20:496–500
33. Roberts RS, Spitzer WO, Delmore T, Sackett DL (1978) An empirical demonstration of Berkson's bias. J Chronic Dis 31:119–128
34. Rodriguez M, Siva A, Cross SA, O'Brien PC, Kurland LT (1995) Optic neuritis: a population-based study in Olmsted County, Minnesota. Neurology 45:244–250
35. Runmarker B, Andersen O (1993) Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. Brain 116(Pt 1):117–134
36. Runmarker B, Andersson C, Oden A, Andersen O (1994) Prediction of outcome in multiple sclerosis based on multivariate models. J Neurol 241:597–604
37. Runmarker B, Martinsson T, Wahlstrom J, Andersen O (1994) HLA and prognosis in multiple sclerosis. J Neurol 241:385–390
38. Salhofer-Polanyi S, Windt J, Sumper H, Grill H, Essmeister M, Diermayr G, Zebenholzer K, Leutmezer F, Zulehner G, Vass K, Asenbaum-Nan S (2013) Benefits of inpatient multidisciplinary rehabilitation in multiple sclerosis. Neuro Rehabilitation 33:285–292
39. Scalfari A, Neuhaus A, Daumer M, Muraro PA, Ebers GC (2014) Onset of secondary progressive phase and long-term evolution of multiple sclerosis. J Neurol Neurosurg Psychiatry 85:67–75
40. Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, Ebers GC (2010) The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain 133:1914–1929
41. Skoog B, Runmarker B, Winblad S, Ekholm S, Andersen O (2012) A representative cohort of patients with non-progressive multiple sclerosis at the age of normal life expectancy. Brain 135:900–911

42. Skoog B, Tedeholm H, Runmarker B, Odén A, Andersen O (2014) Continuous prediction of secondary progression in the individual course of multiple scleosis. Mult Scler Relat Dis 3:584–592
43. Svenningsson A, Runmarker B, Lycke J, Andersen O (1990) Incidence of MS during two fifteen-year periods in the Gothenburg region of Sweden. Acta Neurol Scand 82:161–168
44. Tedeholm H, Lycke J, Skoog B, Lisovskaja V, Hillert J, Dahle C, Fagius J, Fredrikson S, Landtblom AM, Malmestrom C, Martin C, Piehl F, Runmarker B, Stawiarz L, Vrethem M, Nerman O, Andersen O (2013) Time to secondary progression in patients with multiple sclerosis who were treated with first generation immunomodulating drugs. Mult Scler 19:765–774
45. Tremlett H, Paty D, Devonshire V (2006) Disability progression in multiple sclerosis is slower than previously reported. Neurology 66:172–177
46. Tremlett H, Yinshan Z, Devonshire V (2008) Natural history of secondary-progressive multiple sclerosis. Mult Scler 14:314–324
47. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y (2009) Impact of multiple sclerosis relapses on progression diminishes with time. Neurology 73:1616–1623
48. Tremlett H, Zhao Y, Devonshire V (2009) Natural history comparisons of primary and secondary progressive multiple sclerosis reveals differences and similarities. J Neurol 256:374–381
49. Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, May K, Button T, Azzopardi L, Kousin-Ezewu O, Jones J, Compston DA, Coles A (2015) Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry 86:208–215
50. Tutuncu M, Tang J, Zeid NA, Kale N, Crusan DJ, Atkinson EJ, Siva A, Pittock SJ, Pirko I, Keegan BM, Lucchinetti CF, Noseworthy JH, Rodriguez M, Weinshenker BG, Kantarci OH (2013) Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. Mult Scler 19:188–198
51. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, Ebers GC (1989) The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 112(Pt 6):1419–1428
52. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, Ebers GC (1989) The natural history of multiple sclerosis: a geographically based study. I. clinical course and disability. Brain 112(Pt 1):133–146
53. Vukusic S, Confavreux C (2003) Prognostic factors for progression of disability in the secondary progressive phase of multiple sclerosis. J Neurol Sci 206:135–137
54. Yamout B, Itani S, Arabi A, Hamzeh D, Yaghi S (2010) Prognostic factors of multiple sclerosis in Lebanon. Int J Neurosci 120:206–210