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A representative cohort of patients with non-progressive multiple sclerosis at the age of normal life expectancy

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Multiple sclerosis may have a non-progressive symptomatology for decades; however, it is not clear whether the disease activity may abate completely. We identified a cohort of patients, resident in Gothenburg at the time of disease onset, between the years 1950–64 ($n = 307$). These geographical and temporal restrictions, along with favourable conditions for a 'spider' epidemiological study, were optimal for an unbiased selection; this 15-year incidence cohort was essentially followed prospectively for 37–59 years after onset. The shortest follow-up time for patients without primary or secondary progression was 45 years. For patients with an initial relapsing–remitting course and multiple sclerosis diagnosis according to the Poser criteria ($n = 202$), the probability of non-progressive disease after 40 years was 22% (standard error 3.0%), and after 50 years it was 14% (standard error 3.2%). For attack onset including patients with possible multiple sclerosis, the corresponding probabilities after 40 and 50 years were 35% (standard error 3.3%) and 28% (standard error 3.5%), respectively. At the last follow-up in 2009–10, when patients reached the average age of the Swedish population life expectancy, only 13 patients from the multiple sclerosis diagnosis cohort, according to the Poser criteria, remained alive and non-progressive. Their annualized attack frequency diminished with time from 0.29 to 0.015. These patients had been functioning well socially. Nine patients had an Expanded Disability Status Scale score of 0–2.5, and four patients had a score of 3 or 3.5, with deficits dating back to attacks decades ago. Eight patients participated in a complete neuropsychological examination, which showed a slight difference ($P < 0.01$) concerning verbal memory and executive function compared to an age and socially matched reference group, whereas results for five other cognitive domains were within the normal range. Magnetic resonance images fulfilled the Barkhof–Tintoré criteria for multiple sclerosis in 10 of 11 patients, with conspicuously few subcortical lesions relative to extensive periventricular lesions and lesions extending from the inferior midline aspect of the corpus callosum. Prediction of the non-progressive stage was possible with moderate hazard ratios and low sensitivity. Early features that predicted a non-progressive course were complete remission of the onset attack, low or moderate initial relapse frequency and—when the patients with possible multiple sclerosis were included—dominating afferent symptoms. The clinical disease activity had abated in these 13 patients, with the caveat that transition to secondary progression continued to occur after four decades, albeit with decreasing risk.

Keywords: multiple sclerosis; prognosis; disability; cognitive symptoms; MRI
Abbreviations: EDSS = expanded disability status scale

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Introduction

Patients with multiple sclerosis with an inactive disease remaining benign after 4 to 5 decades, with few if any problems from their disease, have little inducement to remain in contact with the neurological health service. To obtain an unbiased evaluation of the frequency of benign multiple sclerosis, it is necessary to use a longitudinal follow-up of an incidence cohort. While several large databases used for natural history studies were geographically confined (Weinshenker *et al.*, 1989; Confavreux *et al.*, 2000; Scalfari *et al.*, 2010), few were incidence cohorts with both geographically and temporally restricted inclusion criteria (Broman *et al.*, 1981; Midgard *et al.*, 1995; Rodriguez *et al.*, 1995). A consensus definition of 'benign multiple sclerosis' was suggested to be 'the patient remaining fully functional in all neurological systems 15 years after disease onset' (Lublin and Reingold, 1996). Several studies refer to benign multiple sclerosis as disease with >10 or 15 years to an Expanded Disability Status Scale (EDSS) of ⩽3 (Ramsaransing and De Keyser, 2006). However, follow-up studies of patients with multiple sclerosis with disease classified as 'benign' after 10 years showed that a large proportion of these patients later converted to a secondary progressive course (Hawkins and McDonnell, 1999; Pittock *et al.*, 2004; Costelloe *et al.*, 2008; Hirst *et al.*, 2008). A progression index was proposed to be better than the EDSS criterion, and secondary progression was found to be a more robust parameter than EDSS (Thompson, 1999; Trojano *et al.*, 2008). There is a general consensus that there is no better predictor for disability than the progressive phase *per se* (Minderhoud *et al.*, 1988; Lublin and Reingold, 1996). As a primary precondition for a benign course is the absence of a progressive phase and most relapses leave only minor residuals, an ultimately benign course must be sought for in the group of patients remaining progression-free. It was previously demonstrated that the overall relapse frequency decreases with time (McAlpine and Compston, 1952; Broman *et al.*, 1981). Here we examine which proportion of patients remain in a non-progressive stage and whether the relapse activity tapers (as predicted) or even abates completely during decades of follow-up, apparently resulting in *formes frustes* ('a disease activity which ceased before development of disability', 'aborted state'). While monophasic multiple sclerosis (clinically isolated syndrome only) may be an extreme case of this type of course, we focus on the possibility of an 'aborted state' in patients with Poser diagnosis. Natural history studies provide relatively consistent information on the proportion of cases with a non-progressive course in the intermediate range. This proportion is ~25% after 25–30 years (Runmarker and Andersen, 1993; Vukusic and Confavreux, 2003; Scalfari *et al.*, 2010). It has recently been questioned whether it is appropriate that patients with low neurological deficit are classified as benign if they have (multiple sclerosis-related) cognitive deficits. In one study, 45% of patients with multiple sclerosis with a disease duration ⩾15 years and EDSS ⩽3 had cognitive deficits (Amato *et al.*, 2006).

The purpose of the present study was: (i) to describe patients with a sustained non-progressive course as extreme variants of a multiple sclerosis incidence cohort, in a material selected on account of its unbiased qualities; (ii) to obtain an unbiased estimate of the proportion of patients with multiple sclerosis remaining non-progressive when reaching the age of normal life expectancy; (iii) to report in detail the neurological, neuropsychological and MRI characteristics of the non-progressive patient group; and (iv) to explore whether the non-progressive condition may be predicted from the clinical features at an early stage.

Materials and methods

Patients

The Gothenburg multiple sclerosis cohort is a population-based incidence cohort of 307 patients with disease onset between 1950 and 1964, who have been and are still followed clinically at the Department of Neurology, Sahlgrenska University Hospital. Case identification procedures, conditions basic to multiple sclerosis registration, and data on multiple sclerosis epidemiology in Gothenburg have been described previously (Andersen, 1980; Broman *et al.*, 1981; Svenningsson *et al.*, 1990; Runmarker and Andersen, 1993; Eriksson *et al.*, 2003). During the incidence period and the following 5 years, all medical records from the Sahlgrenska Neurology Department and out-patient clinic, the only neurological service in the Gothenburg area, were scrutinized for possible multiple sclerosis symptoms (Fig. 1). In the selected cohort, 50% of the patients with initial relapsing–remitting multiple sclerosis were seen at onset and 72% of patients were seen within 3 years of their initial symptoms. Time to endpoint of secondary progression, or EDSS 6, did not differ between cases seen at onset and cases notified later. A prospective record of patients with optic neuritis was obtained from the Department of Ophthalmology at the Sahlgrenska University Hospital.

Classification within the incidence cohort

In the incidence cohort, 255 patients had multiple sclerosis according to the Poser criteria (Poser *et al.*, 1983). Out of these, 52 were autopsy verified, 187 had clinically definite multiple sclerosis and 16 had clinically probable multiple sclerosis, always including clinical episodes or evidence separated in time. Of the 255 patients, 202 had an initial relapsing–remitting course, 44 had a primary progressive course and nine patients could not be clearly assigned to either group (Fig. 1).

Another group of 52 patients did not fulfil the Poser criteria. Of these, 44 had a 'clinically isolated syndrome' and no further clinical activity (referred to as 'possible multiple sclerosis'). Eight had a slowly progressive paraparesis with a CSF enriched oligoclonal IgG reaction (Oppenheim, 1887; Baig *et al.*, 1991). These eight had a complete investigation excluding relevant differential diagnoses (referred to as 'possible progressive multiple sclerosis').

Clinical predictors

Two demographic parameters, age at onset and gender, as well as three attack characteristics, remission of the attack or not, dominating afferent or efferent symptoms, mono- or polyfocal symptoms (Eriksson *et al.*, 2003; Supplementary Table 1), were used as predictors when observed in association with the onset attack or the last attack during the first 5-year period. At the moment, when predictors associated with the onset attack are recorded, the outcome is unknown regarding

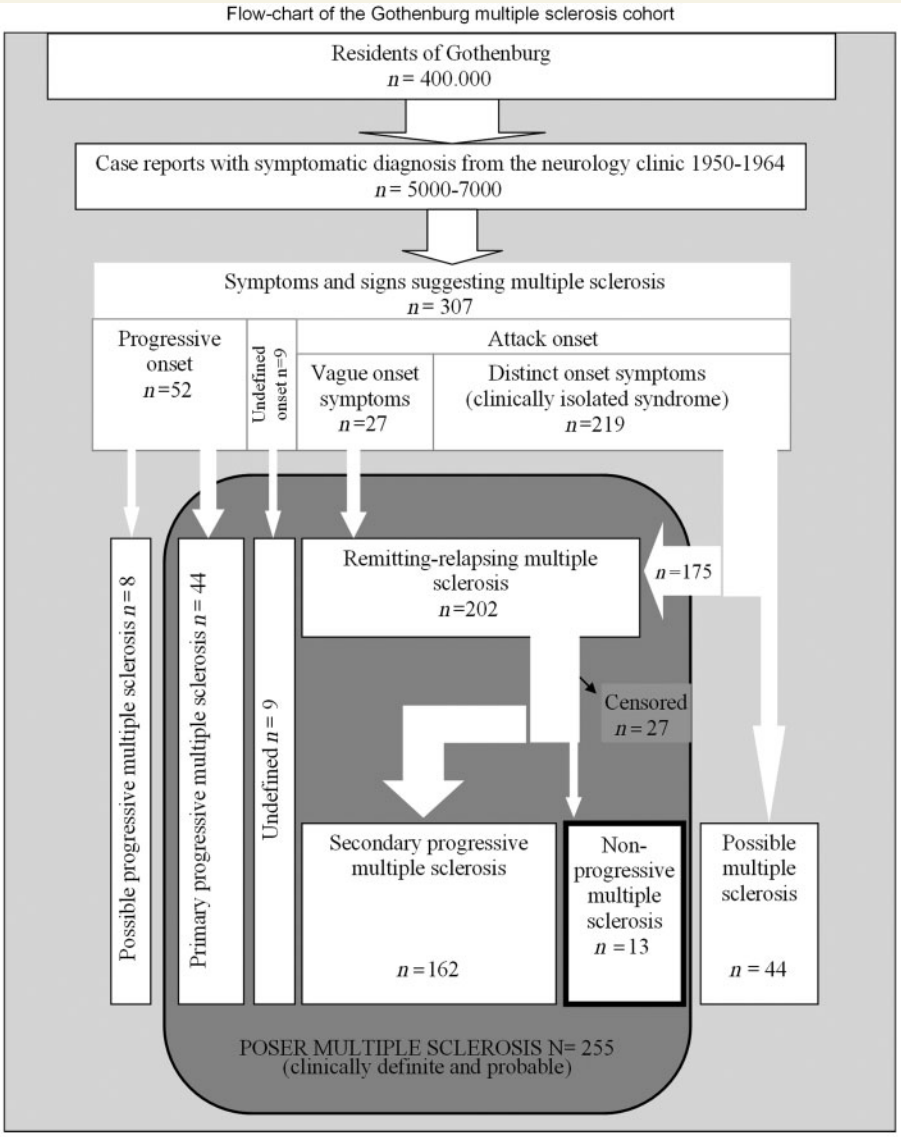

Figure 1 The flow chart shows the successive selection of patients depending on the initial and subsequent clinical evidence. The number of patients with relapsing–remitting multiple sclerosis censored before secondary progression is presented.

final diagnostic status (possible multiple sclerosis or multiple sclerosis according to Poser). To achieve a correct predictive analysis in this situation, possible multiple sclerosis cases must be included in the spectrum of outcome to be evaluated. If, on the other hand, the outcome is limited to patients with multiple sclerosis according to Poser, the input must also be restricted to patients with multiple sclerosis according to Poser diagnosis. Inclusion should then not be initiated until the second attack. A compromise is to include the patients 5 years after onset, provided that they had at least one (diagnostic) relapse and had not entered secondary progression.

Follow-up of the incidence cohort

The present database was derived from two sources. The first source came from examinations of the cohort performed during and after the end of the incidence period. It was performed by the research team (T Broman, L Bergmann, and the present authors O.A., B.R. and B.S.) on three occasions during the first 25 years and on two occasions during the subsequent two decades (Runmarker and Andersen, 1993; Eriksson *et al.*, 2003). The second source came from clinical examinations performed mostly annually, depending on disease activity, at the Department of Neurology. For the first 25 years the database includes a uniquely detailed graphical and numerical record of the deficit of each of the Kurtzke functional systems and a systematic account of the symptoms of each attack. This graphic documentation ($n = 307$) is available on request. For the subsequent 25 years it contains detailed history, type of course, relapses and the hard endpoints EDSS 6, 7 and 10. Treatments other than symptomatic were limited to sporadic steroid- or adrenocorticotropic hormone courses during relapses, in accordance with a restrictive Scandinavian tradition. No long-term immunomodulatory treatment was ever used in this cohort.

Secondary progression was defined as continuous progression for at least 1 year without remission, detectable at time intervals of months or years, but not days or weeks (Lublin and Reingold, 1996) and

recorded at yearly intervals. The number of patients who were alive with a non-progressive course including possible multiple sclerosis by the year 2000 was 61. Of these, 47 were personally examined with assessment of the EDSS (Kurtzke, 1983), 10 were interviewed by telephone, and it was necessary to rely on medical reports for four patients.

Thirteen of the patients with multiple sclerosis diagnosis according to Poser were alive and had a non-progressive course when re-examined in 2009, yielding a minimum follow-up time of 45 years in this category. The median age at follow-up in the non-progressive group for males and females was 71 and 78 years, respectively, approaching the average age of life expectancy of the Swedish population (74 and 80 years; Statistics Sweden, 2011) as well as the average age at death from other diseases (not multiple sclerosis) within this multiple sclerosis cohort (73 and 80 years, respectively).

Of these 13 patients, nine underwent a neuropsychological examination (Table 1). The tests were selected to explore cognitive domains reported to be associated with dysfunction in multiple sclerosis (Chiaravalloti and DeLuca, 2008). The cognitive functions examined consisted of verbal memory, fluency, visuospatial ability, working memory/attention, processing speed, visual memory and executive functions. The examination included the Purdue Pegboard Test, Digit span, Rey Auditory Verbal Learning Test, Rey Complex Figure Test, Digit Symbol, Controlled Oral Word Association Test and the Stroop Test (Lezak, 1995). Normative data were drawn from 50 healthy controls (mean age 75 years, range 70–85 years) in an age-matched subgroup of a previously published normal material (Hellstrom *et al.*, 2007; Nordlund *et al.*, 2008). Following an established procedure (Amato *et al.*, 2006), the fifth percentile of the control performance was used as the cut-off point for calculating the number of failed tests. Patients who scored below this cut-off point in more than two tests were considered cognitively impaired. A Mini-Mental State Examination was performed and the results were compared with age and education-adjusted normative data (Crum *et al.*, 1993). The lower quartile was used as a cut-off score. To estimate IQ, three subtests known to be associated with full-scale IQ in the Wechsler Adult Intelligence Scale (Vocabulary, Picture Completion and Block design) were included, and the results were compared with age-matched normative data (Wechsler *et al.*, 1992). The Epworth Sleepiness Scale (Johns, 1991) and the Beck Depression Inventory (Beck and Steer, 1996) were applied to evaluate daytime sleepiness and depression. None of the patients were taking any medication that could potentially interfere with their neuropsychological performance. The tests were carried out during ~1.5 h by an experienced neuropsychologist (S.W.) in a quiet environment at the Sahlgrenska University Hospital.

Of the 13 non-progressive patients, 11 were examined by MRI of the brain using a standard imaging protocol on a 3 Tesla magnet (Philips Achieva 3.0T) at the Xyrinx facility in Gothenburg. This protocol included axial and sagittal T_1- and T_2-FLAIR (fluid attenuated inversion recovery) weighted images. After the injection of a gadolinium-containing contrast agent (10 ml Multihance), an axial T_2-FSE (fast spin echo) was obtained followed by a coronal 3D-TFE (turbo field echo) and an axial T_1-FLAIR. The evaluation was done by a neuroradiologist (S.E.) according to the recommendations of the multiple sclerosis consortium, using the criteria of Barkhof–Tintoré (Simon *et al.*, 2006), and adding specific observations regarding the corpus callosum.

Statistical methods

The median time to the endpoint (secondary progression) was estimated by Kaplan–Meier analysis using PASW Statistics 18 release 18.0.0. Predictors (Supplementary Table 1) for a particular endpoint which had $P < 0.1$ in the log rank test were selected and tested together in a Cox proportional hazards model (Enter procedure). Patients were censored at death from diseases other than multiple sclerosis, when conditions precluded further evaluation, or at the last complete examination before study termination.

Results

The cohort according to the Poser criteria

Figure 2 shows the probability of reaching progression during the follow-up of the 255 patients with multiple sclerosis according to the Poser criteria. The median time for reaching the progressive course endpoint (including both primary progressive multiple sclerosis and secondary progressive multiple sclerosis) was 8 years [standard error (SE) 0.91]. No patient classified as possible multiple sclerosis after 25 years of follow-up ($n = 33$) (Runmarker and Andersen, 1993) developed any new multiple sclerosis symptoms during the subsequent follow-up until 45 years after onset.

Cases with relapsing–remitting multiple sclerosis/secondary progressive multiple sclerosis

The median time from onset until a diagnostic event according to the Poser criteria in relapsing–remitting multiple sclerosis was 2 years. This diagnostic event was a second distinct attack, the start of a secondary progressive course, or the demonstration of new objective clinical evidence, whichever occurred first. The longest duration observed until a second attack was 24 years.

During the follow-up of the patients with relapsing–remitting multiple sclerosis, 162 patients developed secondary progression. This was characterized by a slowly increasing pyramidal syndrome, which eventually appeared in 156 patients. A pyramidal syndrome with paraparesis as a single initial manifestation occurred in 61 patients, whereas it occurred together with other initial symptoms in 39 patients. Later in the course, secondary progression with paraparesis developed in 56 patients who had an initial manifestation with other symptoms. Other initial solitary manifestations of secondary progression were cerebellar ataxia ($n = 9$), bladder paresis ($n = 16$), cerebral symptoms ($n = 10$), dorsal column ataxia ($n = 4$), or insidious optic neuropathy ($n = 4$). Fifteen patients developed secondary progression >25 years after the onset of multiple sclerosis, the last appearing after 49 years. Twenty-seven patients were censored at various times before the onset of the secondary progressive phase, either because of death unrelated to multiple sclerosis (nine patients; e.g. malignancies, stroke), concurrent disease making evaluation impossible (16 patients; malignancies, stroke, arthritis, dementia), or because the patient declined to participate (two patients). The calculated median time to secondary progression was 12 years (SE 1.11 years). All but two patients with secondary progression had a final EDSS ⩾4.0. These two patients had their last examinations 11 and 12 years after the onset of secondary progression, respectively. One patient

Table 1 The 13 patients with relapsing–remitting multiple sclerosis who had not converted to secondary progression at follow-up in 2009

			Onset attack			First 5 years							Follow-up 2009			MRI 2009						Neuropsychology 2009–10										
							Last relapse*																									
Patient	Gender	Onset age	Monofocal attack	Dominant afferent	Complete remission	Number of relapses	Monofocal attack	Dominant afferent	Complete remission	Total number of relapses	Last relapse, disease year	Oligoclonal bands 2000–04	Disease year	EDSS[b]	Pyramidal score[b]	GD-enhancing	≥ $9T_2$lesions	Infratentorial	Juxtacortical	≥3 periventricular	Corpus callosum	Digit span	RAVLT	RCFT copy	RCFT recall	Purdue pegboard	Stroop A	Stroop B	COWAT	Digit symbol	Total score
197	F	18	√	–	√	2	√	√	√	4	6	NA	45	**0**	0	NA						NA									
311	M	36	√	–	√	0				3	16	NA	48	**0**	0	–	√	–	√	√	√	–	–	–	–	√	√	√	–	√	4
78	F	15	√	–	√	1	–	–	√	9	36	√	48	**0**	0	–	√	–	√	√	√	–	–	–	–	–	–	–	–	–	0
212	F	37	√	√	–	3	√	√	√	8	41	NA	55	**1.5**	1	–	√	√	√	–	–	NA									
87	F	23	√	–		3	–	–	√	12	31	√	57	**2.0**	2	NA						–	–	–	–	√	–	–	–	–	1
29	M	22	√	√	√	1	√	√	–	4	10	–	49	**2.0**	0	–	√	–	√	√	√	–	–	–	–	–	√	√	–	–	2
205[a]	F	33	√	–	√	2	√	–	√	6	12	–	46	**2.0**	1	–	√	√	–	√	√	NA[a]									
261	F	26	√	√	√	0				3	18	√	53	**2.5**	1	–	√	–	–	√	√	–	–	–	–	–	–	–	–	–	0
313	M	27	√	–	√	1	√	–	√	11	37	√	46	**2.5**	2	–	√	–	√	√	√	–	–	–	–	–	–	–	–	–	0
36	F	32	√	–	√	1	√	–	√	3	5	√	45	**2.5**	2	–	√	√	√	√	√	–	–	–	–	√	–	√	–	–	2
317	M	23	√	√	√	0				2	24	√	47	**3.0**	0	–	√	–	√	√	√	–	–	–	–	–	–	–	–	–	0
179	F	33	√	–	√	4	√	–	√	8	15	NA	47	**3.5**	3	–	√	√	√	√	√	–	√	NA[c]	NA[c]	NA[c]	√	–	–	NA[c]	NA[c]
74	F	22	√	–	–	0				2	21	–	54	**3.5**	2	–	√	–	√	√	√	NA									

The left part of the table gives information about the early phase of the disease while the right part concerns the investigations in the years 2009–10. MRI abnormalities in the corpus callosum are not part of the multiple sclerosis criteria but were nevertheless a typical feature. If three or more neuropsychological tests were abnormal (total score), the patient was considered to have a cognitive impairment. MRI could not be performed in one patient because of claustrophobia.

* = last relapse during the first five years.

a Recently developed dementia.

b Impairment due to attacks decades ago.

c Not possible to test due to decreased hand function.

√ = pathological; – = normal; COWAT = Controlled Oral Word Association Test; F = female; M = male; NA = not available or declined; RAVLT = Rey Auditory Verbal Learning Test; RCFT = Rey Complex Figure Test.

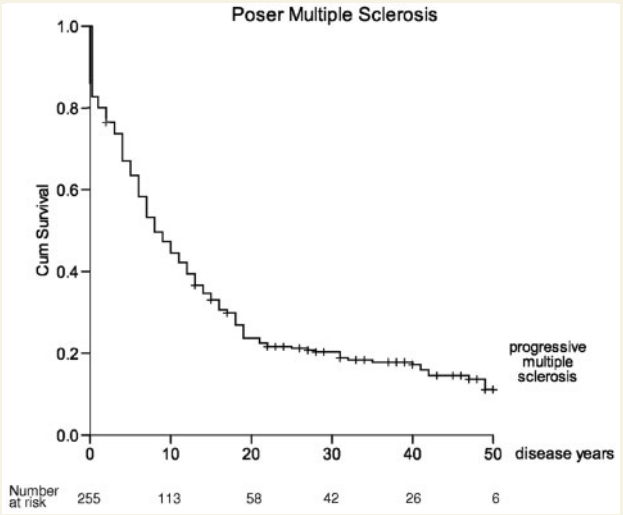

Figure 2 The survival curve shows the decreasing probability of remaining in a non-progressive course during the follow-up in patients with multiple sclerosis according to the Poser criteria. The probability was calculated using the Kaplan–Meier method. The steps on the curve indicate the point in time when one or several individuals reached the endpoint progressive course. The crosses on the lines indicate the point in time for censored observations. In this survival curve, all primary progressive multiple sclerosis cases have their endpoint at time 0. The table below the graph shows the number of patients still at risk for progression during the disease year indicated, e.g. those who had not yet reached the endpoint or been censored.

(with EDSS 3.5) had paraparesis and para-ataxia, and the other patient (with EDSS 2.5) had a slight hemiparesis. Both patients could walk unsupported for at least 500 m.

Non-progressive cases

After 40 years the probability of a non-progressive relapsing–remitting course in multiple sclerosis, according to the Poser diagnosis, was 22% (SE 3.0%; number at risk = 26). After 45 years the probability was 18% (SE 3.0%; number at risk = 18) and after 50 years it was 14% (SE 3.2%; number at risk = 6). The decreasing proportion of non-progressive patients in successive 10-year age groups is reported in Supplementary Table 2.

Clinical features of non-progressive cases with multiple sclerosis according to Poser

Thirteen patients from the 1950–64 incidence cohort were still without signs of secondary progression at the last follow-up in 2009–10, which was after 45–59 years of disease. Ten patients had an EDSS $\leqslant$2.5. Three patients had an EDSS of 3.0–3.5, which had been stable since their last attack, on average three decennia earlier (Table 1). The median number of attacks in these 13 patients was four (range 2–12), and the last attack occurred 18 years (median) after onset, although with large variability (range 5–41). The relapse frequency tapered during the disease course in the 13 patients. During the first 5 years the annualized relapse frequency was 0.29, whereas during years 40–45 it was 0.015 (derived from a single attack). The course was stationary since the follow-up in 2005. All patients had been functioning well socially, apart from one patient who developed Alzheimer's disease. Ten patients had continued to work until they reached retirement age, two were housewives and one patient had retired because of a whiplash injury. However, one had a trigeminal neuralgia, and only one patient was found to have a completely normal neurological (EDSS 0) and neuropsychological status.

Early clinical characteristics of the cases with non-progressive multiple sclerosis, according to Poser

All of the 13 non-progressive cases had a monofocal onset attack, and 10 of the cases had a complete remission of the initial attack. Although the non-progressive patients had a predominance of benign predictors (Eriksson *et al.*, 2003) of the onset attack, no combination of these predictors reached any clinically useful specificity (data not shown).

Cerebrospinal fluid of the cases with non-progressive multiple sclerosis according to Poser

During the years 2000–03, CSF was sampled and analysed using isoelectric focusing and cytology in 9 of the 13 patients characterized as non-progressive by 2009–10. Six of these patients had a CSF enriched oligoclonal IgG reaction. All of the patients had essentially normal values for CSF parenchymal damage markers (neurofilament light, glial fibrillary acidic protein and tau protein), except for the patient who was later diagnosed with Alzheimer's disease, who had increased tau protein levels. Pleocytosis was not observed in any of the cases.

Magnetic resonance imaging of the cases with non-progressive multiple sclerosis according to Poser

MRI was performed on 11 of the non-progressive patients in 2009 (Fig. 3). The findings are summarized in Table 1. None of the patients showed any contrast-enhancing lesions. Lesions in the infratentorial region were uncommon and when present (four patients) only 1–2 small lesions were seen. Periventricular lesions (>3 lesions) were found in all patients but one, and a small number of juxtacortical lesions were found in all but two patients. Multiple lesions extending from the inferior midline aspect of corpus callosum, the calloso-marginal region, were present in all but two patients. These lesions, typical for demyelinating disease, were prominent in some patients. MRI lesions consistent with long-standing multiple sclerosis were seen in all patients but one. This patient had atypical MRI findings, still compatible with multiple sclerosis, with only one true periventricular lesion and several subcortical lesions as well as unusual bilateral juxtacortical lesions in the temporal poles.

Neuropsychology of the cases with non-progressive multiple sclerosis according to Poser

The results of the neuropsychological assessment (n = 10) are summarized in Table 1. One patient had Alzheimer's disease according to the NINCDS-ADRDA criteria (Varma *et al.*, 1999). This patient had visuospatial and executive disturbances. Another patient had decreased hand dexterity that influenced some of the results. In the group of patients able to perform a complete

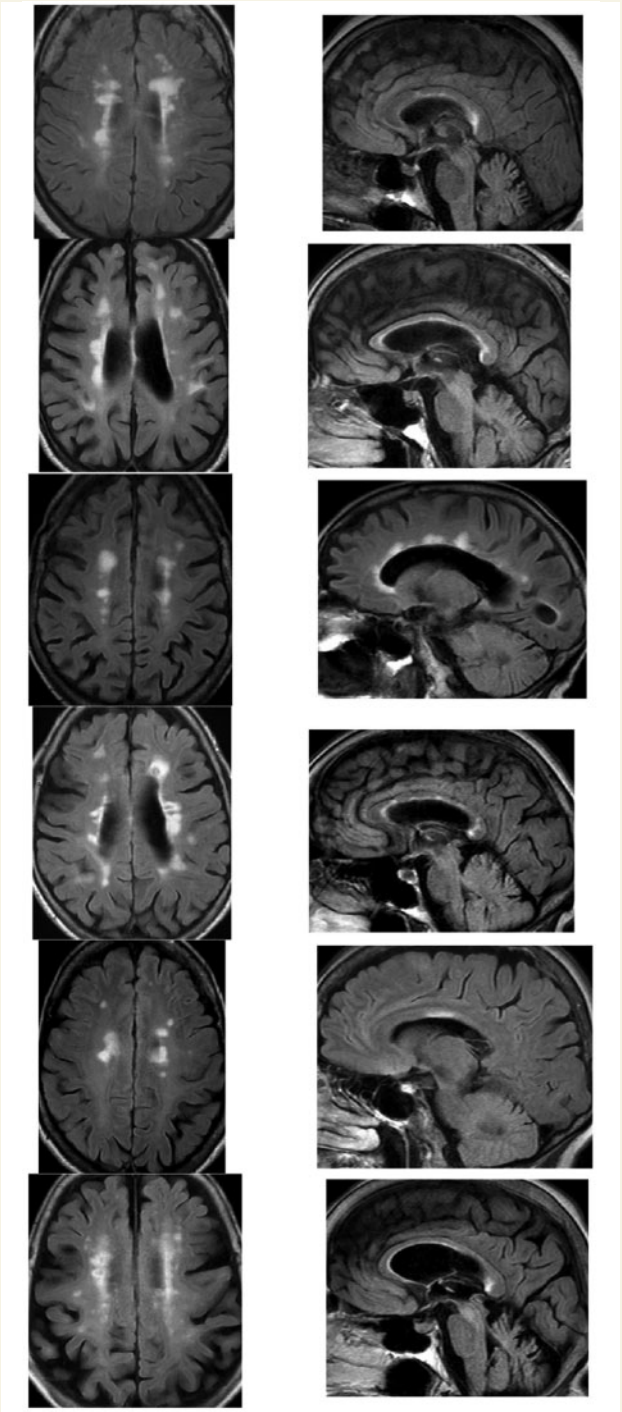

Figure 3 MRI images of patients with relapsing-remitting multiple sclerosis according to the Poser criteria and with a non-progressive disease course at the follow-up 2009. These 12 images are a collage of pairs of representative images from six patients. Each patient is illustrated by two T_2-FLAIR images, one axial along the upper aspect of the lateral ventricular system (*left*) and one sagittal midline view (*right*). White matter lesions are dominantly periventricular, while subcortical lesions are scarce. A summary of the number of lesions is found in Table 1.

evaluable neuropsychological assessment ($n = 8$) only one patient performed below the cut-off score (more than two tests below the fifth percentile) indicating cognitive impairment. However, a significant difference between patients and the control group was found when comparing results on the Rey Auditory Verbal Learning Test ($Z = -3.4$, $P = 0.001$), Stroop A ($Z = -2.9$, $P = 0.004$), and Stroop B ($Z = -2.9$, $P = 0.004$). These tests are mainly associated with verbal memory and executive functions. Patients scored in the normal range on estimates of IQ, and no signs of dementia were detected when scores on the Mini-Mental State Examination were compared with normative data. No patient scored above a cut-off set at 10 for clinical depression (Beck and Steer, 1996). Furthermore, there were no signs of severe daytime sleepiness. All of the patients scored in the normal range on the Epworth Sleepiness Scale (Johns and Hocking, 1997).

Clinically isolated syndrome and no further multiple sclerosis disease activity, possible multiple sclerosis

Of the 44 patients with possible multiple sclerosis, 25 were censored during the follow-up until 2002. Two patients declined follow-up after 1986, and 17 patients were examined in 2002–03. These 17 patients had a median EDSS of 1.0 (range 0–2.5). Six patients had an EDSS of 0. All deficits could be attributed to residual symptoms from the onset attack. During the follow-up before 1985, CSF was investigated in 21 patients using electrophoresis with various methods. Ten of these patients had oligoclonal bands or a CSF enriched gamma globulin fraction.

The probability for a non-progressive multiple sclerosis disease after attack onset (including both relapsing–remitting multiple sclerosis according to Poser and possible multiple sclerosis; $n = 246$) was 35% (SE 3.2) after 40 years and 28% (SE 3.5) after 50 years (Fig. 4).

Prediction of non-progressive outcome

In relapsing–remitting multiple sclerosis, either a low relapse frequency (using a low cut-off <4 during the first 5 years) or a complete remission of the last attack during this period predicted a high probability for a non-progressive course. This result was expressed as the relative risk in the presence of the favourable variant of the dichotomous parameters (Eriksson *et al.*, 2003; Supplementary Table 1). It was obtained with either disease duration (relative risk 0.48, $P = 0.010$ and relative risk 0.37, $P < 0.001$) or age (relative risk 0.37, $P = 0.001$ and relative risk 0.53, $P = 0.008$) at transition to a progressive course as outcome parameter (Tables 2 and 3).

We have reviewed the initial (clinical) diagnosis of the clinically isolated syndrome. The possible multiple sclerosis patients were not systematically examined by MRI, but we consider a complete predictive analysis of all attack onset cases to be essential. Therefore, prediction of the non-progressive outcome was also assessed from the onset including relapsing–remitting and possible multiple sclerosis (Tables 4 and 5). Under these conditions, a complete remission and afferent symptoms of the onset attack

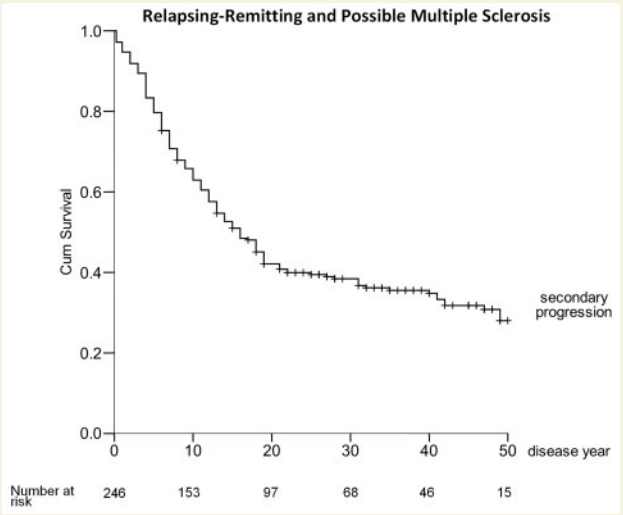

Figure 4 The survival curve shows the decreasing probability of remaining in a non-progressive course during the follow-up including patients with relapsing-remitting multiple sclerosis according to the Poser criteria and patients with possible multiple sclerosis (no further evidence of clinical activity after the first attack). The probability was calculated using the Kaplan–Meier method. The crosses on the lines indicate censored observations. The table below the graph shows the number of patients still at risk for progression during the disease year indicated.

predicted a higher probability for a non-progressive course (relative risk = 0.66, $P = 0.008$ and relative risk = 0.61, $P = 0.003$). Gender, age at the onset attack or polyfocal lesions did not predict the disease course.

Discussion

The variation in multiple sclerosis prognosis is huge, an issue almost as important as the diagnosis itself. Charcot (1877) described 'formes frustes' (abortive cases) of multiple sclerosis and mentioned the 'possibilité de la guérison' (the possibility of spontaneous healing). This strictly framed question has never received an unambiguous answer. We report here results that probably approach the ultimate answer, as there has never been and probably never will be other material matching the stringency of inclusion and longitudinal follow-up as the present incidence cohort, which is essentially untreated. We observed that 14% of patients with Poser multiple sclerosis diagnosis and an initial relapsing–remitting course had a 'benign' course, in the sense of freedom from progression, >45 years after onset.

The definition of 'benign' multiple sclerosis

Definitions based on EDSS were used for short- or intermediate follow-up. Benign multiple sclerosis was defined as EDSS ⩽2 after

Table 2 Prediction of secondary progression from the first 5 years in a subgroup of patients with remitting-relapsing multiple sclerosis with no progression and at least one relapse in this period

Predictors	Number of patients in the subgroups (median 75th percentile)	Endpoint—secondary progression			
		Disease years from Year 5	*P*-value	Age	*P*-value
Total subgroup	$n = 86$	8 (1.0)		45 (1.5)	
Relapse frequency during first 5 disease years	1–3 relapses ($n = 68$) ⩾4 relapses ($n = 16$)	9 (1.3) 4 (1.6)	0.045	46 (1.8) 33 (4.2)	<0.001
Degree of remission of the last relapse in the first 5 years	Complete ($n = 46$) Incomplete ($n = 40$)	13 (1.7) 4 (0.8)	<0.001	44 (2.0) 46 (3.9)	0.03
Monofocal affection in the last relapse	Monofocal ($n = 74$) Polyfocal ($n = 12$)	9 (1.3) 2 (0.6)	0.27	45 (1.8) 41 (5.2)	0.37
Dominantly afferent affection in the last relapse versus motor or mixed affection	Afferent ($n = 27$) Rest ($n = 59$)	12 (3.4) 8 (0.9)	0.122	44 (6.1) 45 (1.6)	0.48
Pure afferent affection in the last relapse versus major motor affection	Afferent ($n = 51$) Motor ($n = 33$)	9 (1.4) 7 (2.4)	0.145	44 (2.3) 45 (1.7)	0.65
Monofocal affection in the last relapse according to neuroanatomy	Optic neuritis ($n = 10$) Brain stem ($n = 16$) Spinal cord ($n = 30$)	8 (2.6) 7 (2.0) 9 (2.1)		35 (4.9) 41 (2.4) 38 (1.7)	
	ON versus BS		0.29		0.42
	ON versus SP		0.87		0.76
	BS versus SP		0.27		0.26

The median time in years are presented with corresponding standard errors in brackets.
P-values from log-rank tests are presented. Gender was not a significant predictor.
BS = brain stem lesion; ON = optic neuritis; SP = spinal cord lesion.

10 or 15 years (Gauthier *et al.*, 2009; Glad *et al.*, 2010), EDSS ⩽3 after 10 or 15 years of disease (Lublin and Reingold, 1996; Hawkins and McDonnell, 1999; Amato *et al.*, 2006; Sayao *et al.*, 2007; Costelloe *et al.*, 2008; Portaccio *et al.*, 2009; Mastorodemos *et al.*, 2010) or fully functional in all systems after 15 years (Lublin and Reingold, 1996; Benedetti *et al.*, 2009). Follow-up studies of patients with multiple sclerosis with disease classified as 'benign' after 10 years showed that a large proportion of these patients later converted to a secondary progressive course (Hawkins and McDonnell, 1999; Pittock *et al.*, 2004; Costelloe *et al.*, 2008; Hirst *et al.*, 2008). An EDSS level ⩽2 had stronger prognostic implications for a benign course (Pittock *et al.*, 2004; Sayao *et al.*, 2007). However, there is a random factor in the score of residuals after a series of relapses (Liu and Blumhardt, 2000). EDSS at one point in time may have very different implications. A low EDSS during the initial phases of a progressive course cannot be taken as supporting a benign disease. Residual EDSS scores after attacks vary with random factors. The strongest predictor of future disability is a progressive course. We propose that the criterion of long-term inactivity or apparent cessation of disease activity is more relevant as a definition of benign multiple sclerosis, at least for long follow-up times. We suggest that a more important and probably immunologically relevant divider is between long-term inactive and progressive disease, irrespective of the findings of various slight deficits from relapses decades ago. We believe this is a reasonable clinical correlate to immunopathology and immunogenetics.

Table 3 Prediction of secondary progression. Cox regression analysis from the first 5 years in the subgroup of patients with remitting-relapsing multiple sclerosis with no progression and at least one relapse in this period

Predictors	Sig.	Relative risk	95.0% CI	
			Lower	Upper
Disease year				
1–3 versus ⩾4 relapses	0.010	0.477	0.271	0.838
Complete remission	0.000	0.371	0.230	0.596
Age				
1–3 versus ⩾4 relapses	0.001	0.368	0.210	0.647
Complete remission	0.008	0.525	0.326	0.847

Cox regression using enter selection. The predictors for a particular endpoint were analysed together. The predictors included were those with $P < 0.1$ in the log-rank test (Table 2).
CI = confidence interval.

The ultimately 'benign' cases with multiple sclerosis diagnosis according to Poser

Even these uniquely benign patients were slightly marked by the disease. Three of our 13 patients had EDSS of 3 or 3.5 by 2009. However, these deficits were essentially identical to findings at previous examinations. The follow-up investigation confirmed the absence of ongoing disease activity, and the minor neurological

Table 4 Prediction of secondary progression from the first attack in patients with attack onset including relapsing–remitting and possible multiple sclerosis

Predictors	Number of patients in the subgroups (median 75th percentile)	Endpoint—secondary progression			
		Disease years from onset attack	*P*-value	Age	*P*-value
The whole subgroup	*n* = 246	16 (1.5)		48 (1.8)	
Gender	Male (*n* = 83)	15 (2.5)	0.26	45 (1.6)	0.28
	Female (*n* = 163)	18 (1.8)		51 (2.8)	
Degree of remission	Complete (*n* = 154)	19 (2.3)	0.005	46 (2.1)	0.08
	Incomplete(*n* = 92)	11 (1.9)		50 (3.3)	
Monofocal affection	Monofocal (*n* = 227)	16 (1.6)	0.24	49 (2.3)	0.11
	Polyfocal (*n* = 19)	7 (3.3)		39 (1.5)	
Dominantly afferent affection versus motor or mixed affection	Afferent (*n* = 150)	22 (7.7)	0.002	53 (9.4)	0.008
	Rest (*n* = 96)	13 (1.4)		46 (1.7)	
Pure afferent affection versus major motor affection	Afferent (*n* = 60)	35 (12.0)	<0.001	70 (8.8)	0.004
	Motor (*n* = 73)	11 (2.7)		46 (2.6)	
Monofocal affection according to neuroanatomy	Optic neuritis (*n* = 61)	41 (12.4)		68 (10.5)	
	Brain stem (*n* = 44)	18 (3.2)		47 (4.1)	
	spinal cord (*n* = 49)	15 (2.9)		49 (3.4)	
	ON versus BS		0.18		0.18
	ON versus SP		0.24		0.52
	BS versus SP		0.95		0.46

The median time in years are presented with corresponding standard errors in brackets.
P-values from log-rank tests are presented.
Gender and age at the onset attack were not significant predictors.
BS = brain stem lesion; ON = optic neuritis; SP = spinal cord lesion.

Table 5 Prediction of secondary progression. Cox regression from the first attack in patients with attack onset including possible multiple sclerosis (no clinical multiple sclerosis disease activity after the first attack)

Predictors	Sig.	Relative risk	95.0% CI	
			Lower	Upper
Disease year				
Complete remission	0.008	0.66	0.48	0.90
Dominant afferent affection	0.003	0.61	0.44	0.85
Age				
Complete remission	0.12	0.78	0.57	1.07
Dominant afferent affection	0.01	0.66	0.47	0.91

Cox regression using enter selection. The predictors for a particular endpoint were analysed together. The predictors included were those with $P < 0.1$ in the log-rank test (Table 4).
CI = confidence interval.

signs could be traced back to distant attacks. There was no historic corollary to the minor neuropsychological deficits. Concerning cognitive performance, a majority (seven of eight fully evaluable patients) of the non-progressive patients performed within the normal range in the present study. Supporting an essentially preserved cognitive ability, all but one of our 'benign' patients had continued to work, either until retirement age in a professional occupation or as housewives (two patients), and all were socially well established. These results deviate from a study closer in time to the active multiple sclerosis disease (Amato *et al.*, 2006) where half of the patients in their benign multiple sclerosis group performed with significant cognitive impairment. Neuropsychological dysfunction was a predictive factor in relapsing–remitting multiple sclerosis (Eriksson *et al.*, 2003; Portaccio *et al.*, 2009). Thus, the non-progressive subgroup in the present study may represent a selected subgroup of patients who are both neurologically and neuropsychologically benign, with cognitive function preserved throughout their course. Supporting this notion, patients with longstanding benign multiple sclerosis (EDSS $\leqslant$3 after 25 years) had less fatigue and infrequent cognitive impairment compared with patients who had EDSS progression (Sayao *et al.*, 2011).

The 13 non-progressive patients in the present study had no previous MRI. However, the MRI performed after 45 years fulfilled the Barkhof criteria (Simon *et al.*, 2006) in all patients but one. The callosal and periventricular lesions were extensive compared with the small number of lesions in the subcortical area, where new lesions tend to be located according to previous experience (Kidd *et al.*, 1999). Calloso-septal lesions are highly specific for multiple sclerosis, and it is very unusual for cerebrovascular lesions to involve the callosum without including the contiguous structures (Uchino *et al.*, 2006). Published MRI findings from patients with benign multiple sclerosis show similarities to the images shown in the present study (Fig. 3). While patients with benign multiple sclerosis were reported to have a lesion burden comparable to that in patients with secondary progression, the frequency of cervical cord lesions was lower, and also the rate of development of enhancing lesions was lower (Rovaris *et al.*, 2009). A subgroup of patients with benign multiple sclerosis who had MRI lesions similar to patients with secondary progression had cognitive impairment, while patients with benign multiple sclerosis without cognitive impairment had fewer MRI lesions (Rovaris *et al.*, 2008). Follow-up studies from the clinically isolated syndrome have revealed a number of 'MRI only multiple sclerosis' cases (Chard *et al.*, 2011). However, no MRI follow-up of multiple sclerosis patients to the age of population life expectancy has been published. The present study shows that patients with multiple sclerosis according to Poser without clinical disease activity for many years and near normal cognitive performance may have extensive MRI lesions.

The definition of the incidence cohort

The most unbiased and representative type of patient cohort was reported to be the incidence cohort (Sackett, 1991; Kurland, 1994). There is a considerable amount of censoring with this length of follow-up, but the main causes of censoring in multiple sclerosis are generally neutral, unassociated with the course of multiple sclerosis (Koch-Henriksen *et al.*, 1998; Bahmanyar *et al.*, 2009). Therefore, censoring at death from other diseases should not influence the risks calculated for multiple sclerosis endpoints using the Kaplan–Meier method. It is essential, not least for long-term follow-up, to maintain full control of databases not only concerning selected outcome parameters but also for censoring. Failure to notify deaths in other diseases will result in erroneously long calculated time to outcome. The present database was coordinated with the Swedish 10-digit personal coding system and the national cause of death register. The cause of deaths were classified as caused by multiple sclerosis (EDSS 10), other diseases (censoring) or combined (EDSS 10 could be default). Recently, a higher prevalence of multiple sclerosis than that of the Gothenburg 1950–1964 incidence cohort was reported (Ahlgren *et al.*, 2011). Probably the higher prevalence of multiple sclerosis reported results from the present general use of the more permissive McDonald (MRI-based) diagnostic criteria (Polman *et al.*, 2011), from increased survival, and from increased awareness of cases with less typical symptomatology (differential diagnosis against psychiatric, vascular or rheumatological diseases). It remains to be determined whether such 'atypical' cases could have a benign outcome.

In the present report, we follow the tradition from previous natural history studies to use the Poser diagnostic criteria. When we predict a non-progressive course in this cohort we prefer to exclude cases with primary progressive multiple sclerosis, since the predictors would be confounded with, and mainly identify, cases with primary progressive characteristics, such as older age, male gender, no remission of onset attack and motor symptoms (Weinshenker *et al.*, 1989). Furthermore, findings concerning the possible multiple sclerosis category should be reported separately, taking their particular and delicate diagnostic problems into consideration.

Can the disease activity abate completely?

The disease activity may abate completely after an initial phase with activity manifested as relapses. The present study shows that the ultimate 'possibilité de la guérison' for a lifetime is a clinical

reality, however individually elusive. Transition to the secondary progressive phase continues to occur after four decades, although the risk decreases with time (Runmarker *et al.*, 1994). Sporadic attacks still appear although with decreasing frequency. The prognostic significance of the CSF enriched oligoclonal IgG reaction found in half of these patients, indicating persisting inflammatory activity, is not clear. In the future, sensitive methods may show whether subtle neurodegenerative and even immunological processes are still at play in the patients who experience the 'guérison'.

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Supplementary material

Supplementary material is available at *Brain* online.

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