MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Predicting the profile of increasing disability in multiple sclerosis

Valentina Tomassini, Fulvia Fanelli, Luca Prosperini, Raffaella Cerqua, Paola Cavalla and Carlo Pozzilli

Multiple Sclerosis Journal

2019, Vol. 25(9) 1306–1315

DOI: 10.1177/1352458518790397

Abstract

Background: Effective therapeutic strategies to preserve function and delay progression in multiple sclerosis (MS) require early recognition of individual disease trajectories.

Objectives: To determine the profiles of disability evolution, identify their early predictors and develop a risk score of increasing disability.

Methods: We analysed demographic, clinical and magnetic resonance imaging (MRI) data from patients with relapsing MS, Expanded Disability Status Scale (EDSS) score of 3.0–4.0 and follow-up ≥ 2 years. Attaining EDSS = 6.0 defined *increasing disability*; relapses and/or MRI defined disease *activity*.

Results: In total, 344 out of 542 (63.5%) patients reached EDSS ≥ 6.0; of these, 220 (64.0%) showed disease activity. In patients with activity, the number of relapses before reaching EDSS 3.0–4.0 predicted increasing disability; age > 45 at baseline predicted increasing disability without activity. Combining age and number of relapses increased the risk of and shortened the time to EDSS = 6.0.

Conclusion: Increasing disability is frequently associated with persistent activity. The high number of relapses identifies early those patients worsening in the presence of activity. Age predicts increasing disability in the absence of activity. The presence of both factors increases the risk of developing severe disability. As this study likely describes the transition to progression, our findings contribute to improving patient management and stratification in trials on progressive MS.

Keywords: Multiple sclerosis, disability, MRI, relapse, age, predictors

Date received: 26 January 2018; revised: 16 June 2018; accepted: 27 June 2018

Correspondence to:
V Tomassini
Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University and University Hospital of Wales, Heath Park Campus, Cardiff CF14 4XN, UK.
tomassiniv@cardiff.ac.uk

Valentina Tomassini
Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University and University Hospital of Wales, Cardiff, UK

Fulvia Fanelli
Carlo Pozzilli
Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

Luca Prosperini
Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy/Department of Neurosciences, San Camillo-Forlanini Hospital, Rome, Italy

Raffaella Cerqua
Neurological Clinic, Marche Polytechnic University, Ancones, Italy

Paola Cavalla
Department of Neurosciences, City of Health and Science University Hospital of Turin, Turin, Italy

Valentina Tomassini and Fulvia Fanelli contributed equally to this manuscript.

Introduction

Challenges in the management of multiple sclerosis (MS) progression stem from uncertainty over its diagnosis and the main pathological substrate, both of which remain unknown in the individual case. This makes early identification of disease trajectories difficult and the therapeutic targets unclear, resulting in unguided and largely ineffective treatment decisions.

Given the challenge in recognising the progressive course at inception, the diagnosis of progression is retrospective.[1] However, the early phase of the disease can already suggest the risk of subsequent progression.[2,3] Pharmacological studies suggest that, while on treatment, the accumulation of disability, which, when confirmed and progressive, represents also the clinical measure of progression, is influenced by the pretreatment characteristics of MS.[4,5]

The revised classification of MS phenotypes has underlined the importance of inflammation as a pathological substrate throughout the disease evolution and across disease subtypes.[1] In line with this classification, evidence from clinical trials confirms that inflammation is a major pathological substrate in the progressive phase of MS.[6] Its role is so significant in determining and supporting progression that inflammation is both a predictor of increasing disability[4] and a therapeutic target in progressive MS.[7]

Closely related to inflammation is neurodegeneration, which is recognised as a major pathological hallmark of MS progression[8] and a target of treatments.[9] The relationship between neurodegeneration and inflammation in MS remains elusive. While neuropathology suggests that neurodegeneration results from inflammation, it

also indicates that local anatomical factors, such as cortical folding and brain vasculature, determined by the individual brain structure[8] and influenced by aging,[10,11] can play a role.

In this study, we aim to (1) quantify the proportion of patients belonging to the disease courses defined in the revised classification of MS phenotypes,[1] (2) identify early predictors of such courses to recognise early the disease trajectory at an individual level and, among patients with increasing disability, (3) define a risk score of such increase, based on initial individual characteristics. Firstly, we identify the patterns of disability changes from moderate to severe. Secondly, we investigate predictors of different profiles of increasing disability to identify early the main contributors to disease evolution in individual patients. Finally, we combine these predictors into a score that stratifies the risk of disability evolution and aids an early recognition of the individual disease trajectory, with implications for both clinical and research practice.

Materials and methods

Patients

We retrospectively studied patients attending three Italian MS Centres (Sant'Andrea Hospital, Sapienza University of Rome; Ospedali Riuniti, Marche Polytechnic University of Ancones; San Giovanni Battista Hospital, University of Turin).

Eligibility criteria included a diagnosis of MS[12] with relapsing onset,[1] a baseline Expanded Disability Status Scale (EDSS) score between 3.0 and 4.0 and a minimum time of observation subsequent to the attainment of EDSS 3.0–4.0 equal to 2 years. The starting EDSS of 3.0–4.0 was chosen to select a cohort likely to experience disability changes over the observation period as a result of disease progression.[13] The duration of the follow-up was chosen in agreement with previous studies on progressive MS[14,15] and in order to be able to confirm increasing disability with at least two EDSS assessments performed 1 year apart.[1] Patients taking disease-modifying therapies (DMTs) were included, as these data were collected as part of the routine clinical monitoring and, for ethical reasons, we could not withhold treatment in eligible patients.

During the study, patients were followed up with clinical assessments, which included EDSS scoring, recording of the number of relapses and magnetic resonance imaging (MRI) monitoring.

The local ethics committees approved the study. Participants provided informed consent. The study was conducted according to the Declaration of Helsinki.

Study design and measurements

Data collection started in October 1997 and ended in December 2015. At database lock (December 2015), the combined dataset of screened patients across Centres included 2872 patients. Of these, we extracted those with the above-mentioned eligibility criteria. Patients were followed up from EDSS 3.0–4.0 (baseline) until they reached an EDSS of 6.0 or until the end of the observation period. The following data were collected at baseline: age, sex, type of MS onset (mono- or multifocal), the interval between the first (clinically isolated syndrome) and the second episode (first relapse), the time to the attainment of EDSS 3.0–4.0, the number of relapses before reaching EDSS 3.0–4.0 and the exposure to DMTs before reaching an EDSS of 3.0–4.0. Licensed DMTs, including interferon beta, glatiramer acetate, fingolimod and natalizumab, as well as off-label treatments (e.g. including mitoxantrone, azathioprine, cyclophosphamide), were all allowed. We also calculated the number of patients with gadolinium (Gd)-enhancing lesions in the brain and/or in the spinal cord MRI scans. All the patients had a pre- and post-contrast MRI scan performed within 6 months of baseline assessment (EDSS 3.0–4.0).

During the follow-up period, we quantified the time (number of years) necessary to reach an EDSS$\geq$6.0, confirmed in two subsequent neurological examinations performed 1 year apart. MS specialists, routinely involved in clinical trials, quantified the EDSS scores.

We also calculated the number of relapses and the number of patients with Gd-enhancing lesions in the brain and/or in the spinal cord from MRI scans performed yearly until the attainment of an EDSS$\geq$6.0 or until the end of the observation. These scans were sampled from the routine pre- and post-contrast MRI scans that were planned according to the patient's treatment and ranged from one MRI every 6 months to one MRI every 4 months. We based our measure of MRI activity on the presence/absence of activity and thus on the number of 'active' or 'inactive' patients, which is a robust measure when dealing with clinical scans. We considered the number of relapses, rather than the relapse severity or the contribution of single relapses to the outcome, given that the majority of patients were likely to be on DMTs and DMTs may change the relapse severity and outcome.[13] Patients

were assessed clinically, if a relapse was suspected. *Disease activity* was defined as the occurrence of relapses and/or Gd-enhancing lesions on the MRI scan. These measures, along with demographics and other clinical data, were used to predict the attainment of the outcome measure.

Outcome measure

Our *outcome measure* was the change in EDSS score from 3.0–4.0 to 6.0 or more during the observation period. EDSS≥6.0 is considered as a landmark of irreversible disability.[16] This EDSS change was chosen as an objective, robust, clinically meaningful evolution of disability, which is likely to include the shift from the relapsing to the progressive phase and thus to reflect disease progression within the disability range used here.[13,16]

Statistical analysis

Demographic and clinical data were described as mean ± standard deviation (SD) or median (range) and count (proportion), as appropriate. Before entering further statistical analysis, baseline data were checked for outliers and outlying subjects were excluded.

Firstly, we estimated the number of patients who reached the disability outcome according to whether they had disease activity or not. The Fischer's exact test was performed to test whether disease activity could affect the proportion of patients reaching the disability outcome. Secondly, the log-rank test was performed to explore whether there was any difference in the time to reach the disability outcome between patients with and without disease activity. Thirdly, after estimating the proportions of patients with increasing disability experiencing (group D) or not (group C) disease activity, and without increasing disability experiencing (group B) or not (group A) disease activity, we tested for differences between the groups using the Chi-square test (categorical variables) or one-way analysis of the variance (ANOVA; continuous variables), with Bonferroni post hoc test comparisons. Fourthly, potential predictors for the risk of attaining the disability outcome were investigated by performing Cox proportional hazard models (stratified by site) in the whole sample and separately in patients with and without disease activity. Age, sex, time to the first relapse, time to reach EDSS of 3.0–4.0 (i.e. disease duration), number of relapses before reaching EDSS of 3.0–4.0, mono- or multifocal onset, presence of Gd enhancement at baseline (i.e. at the time of EDSS 3.0–4.0) and the presence of DMTs entered the Cox models as independent variables. Continuous variables at baseline (age at EDSS of 3.0–4.0, time to first relapse, time to reach EDSS 3.0–4.0, number of relapses prior to reaching an EDSS of 3.0–4.0) were categorised into tertiles. The follow-up period was calculated as the time elapsed from EDSS 3.0–4.0 to the attainment of EDSS 6.0. Whenever the outcome of EDSS≥6 had not been reached, the last available EDSS assessment was considered. Finally, we modelled a composite risk score for experiencing a confirmed increase in disability based on the results of the Cox proportional hazard models derived from the two different patient groups (with and without disease activity). For each patient, this composite score was estimated by summing up the number of existing risk factors in that subject. A further Cox regression model was then run to explore whether the composite risk score could be suitable to discriminate patients with different risk of disability outcome. p values less than 0.05 (two-sided) were considered as significant.

Data were analysed using SPSS 16.0 software (IBM SPSS, Chicago, IL, USA).

Results

Baseline characteristics

Out of 615 MS patients who fulfilled the eligibility criteria, 542 patients survived the outlier detection and thus entered the analysis (300 (55%) from Rome, 138 (26%) from Ancones and 104 (19%) from Turin). Table 1 reports the baseline demographic, clinical and MRI characteristics of the patients, all of whom were on DMTs.

Increasing disability during the follow-up

During the follow-up, 344 (63%) patients reached an EDSS≥6.0, while 198 (37%) patients did not (Figure 1). Within each group, the proportion of patients with disease activity was not significantly different from that of patients without disease activity ($p=0.14$, Fischer's exact test; Figure 1). Within the group with increasing disability, the mean ± SD values of the number of years necessary to reach an EDSS≥6.0 from an EDSS of 3.0–4.0 were 6.4 ± 2.8 in the group of patients with disease activity and 6.4 ± 3.3 in the group without disease activity ($p=0.24$, log-rank test). The presence of DMTs overall did not affect the attainment of EDSS 6.0, although high-efficacy treatments at the time of EDSS 3.0–4.0 were subsequently associated with a significantly lower proportion of patients experiencing increasing disability during the study (Table 2).

Table 1. Cohort characteristics.

Characteristics	Values ($n=542$)
Age, years	41.8 (8.5)
Sex, no. of women (%)	365 (67.3%)
No. of patients (%) with multifocal onset	116 (21.4%)
Time to first relapse after CIS, years	2.6 (2.7)
Time to reach EDSS of 3.5±0.5, years	11.7 (6.6)
No. of relapses before reaching EDSS 3.5±0.5	5.8 (3.5)
No. of patients (%) with Gd-enhancing lesions at entry	243 (39.5%)
No. of patients (%) with MS-specific treatment at study entry	
Interferon beta or copaxone	352 (65.0%)
Natalizumab	96 (17.7%)
Immunosuppressants	94 (17.3%)
Study follow-up, years	6.3 (3.1)

CIS: clinically isolated syndrome; Gd: Gadolinium; EDSS: Expanded Disability Status Scale.
Values are mean (SD), unless indicated otherwise.

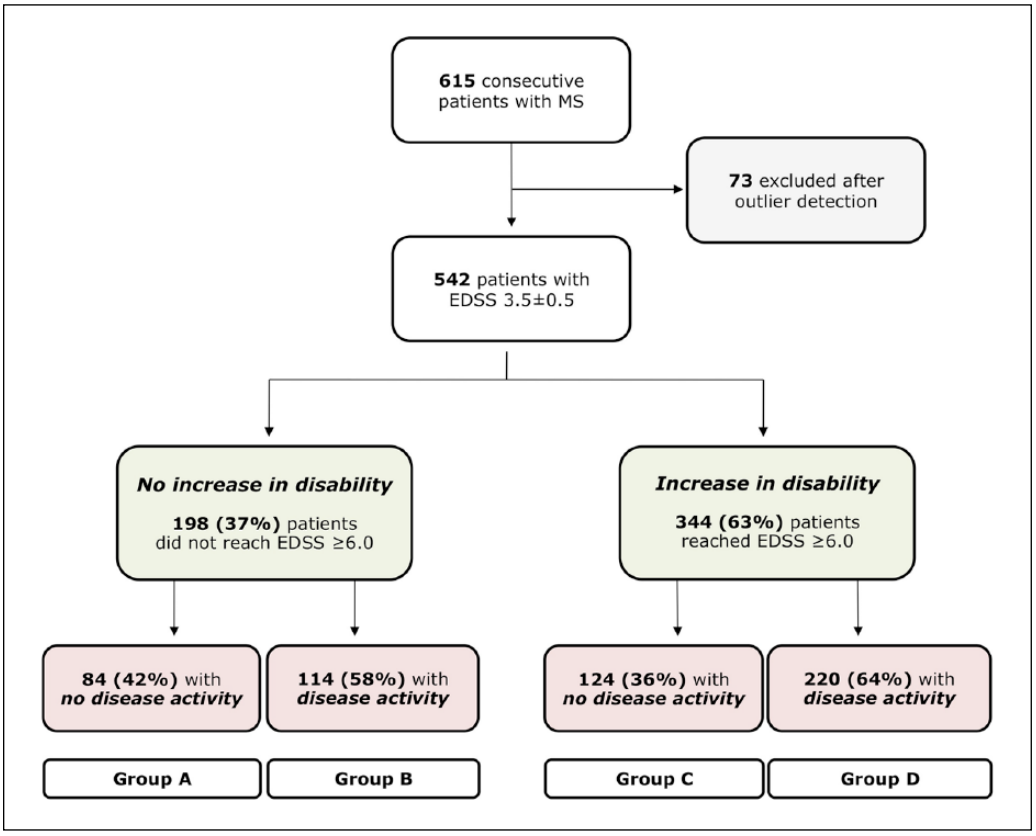

Figure 1. MS patients reaching the outcome (EDSS≥6.0) or ending the follow-up before attaining it. Disease activity was defined as the occurrence of relapses or enhancing lesions on the MRI scan. Over a mean±SD observation period of 6.3±3.1 years, the majority of patients attained an EDSS≥6.0, mainly in association with disease activity. The four groups defined by the attainment of the disability outcome in the presence or absence of disease activity are indicated as groups A, B, C and D.

There was a significant difference in age, time to reach EDSS 3.0–4.0, number of relapses before reaching EDSS 3.0–4.0 and the presence of Gd enhancement at study entry among the four groups of

Table 2. Proportion of MS patients experiencing increasing disability over the follow-up by MS-specific treatment at study entry.

	Interferon beta or glatiramer acetate ($n=352$)	Immunosuppressants ($n=94$)	Natalizumab ($n=96$)
No. of patients with increasing disability (EDSS≥6.0)	234 (66%)	60 (64%)	50 (52%)*
Median (SD) follow-up, years	6.6 (3.2)	6.3 (2.8)	5.0 (2.1)**

MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; SD: standard deviation.
*$p=0.03$ by Chi-square test.
**$p<0.001$ by one-way ANOVA.

Table 3. Baseline characteristics of patients stratified for disease activity and increasing disability.

Characteristics	MS patients without increasing disability		MS patients with increasing disability		Between-group differences
	No activity (group A), $n=84$	Activity (group B), $n=114$	No activity (group C), $n=124$	Activity (group D), $n=220$	p
Age, years	41.3 (8.1)	40.2 (9.1)	45.2 (8.2)	40.8 (8.0)	<0.001*
Sex, no. of women (%)	53 (63)	80 (70)	84 (68)	148 (67)	0.77
Time to first relapse, years	2.6 (2.6)	2.3 (2.6)	3.1 (3.0)	2.4 (2.6)	0.10
Time to reach EDSS 3.5±0.5, years	11.3 (6.3)	10.5 (6.7)	13.9 (6.8)	11.3 (6.4)	<0.001*
No. of relapses before reaching EDSS 3.5±0.5	4.8 (2.7)	5.5 (2.8)	5.5 (3.3)	6.5 (3.9)	<0.001**
Multifocal onset, *n* (%)	20 (24)	24 (21)	28 (23)	44 (20)	0.88
No. of patients (%) with Gd-enhancing lesions at entry	27 (32)	59 (52)	28 (23)	101 (46)	<0.001°
Study follow-up, years	6.5 (4.0)	6.4 (3.2)	6.7 (3.8)	6.5 (3.7)	0.64

MS: multiple sclerosis; EDSS: Expanded Disability Status Scale.
Values are mean (SD), unless indicated otherwise. A, B, C and D indicate the groups of patients on the basis of the presence or absence of disease activity and increasing disability (see section 'Results' and Figure 1).
After Bonferroni post hoc tests, *$p<0.05$, C versus A, B, D; **$p<0.05$, D versus A; °$p<0.05$, B and C versus A and D.

patients (all p values < 0.001; Table 3). Post hoc analysis indicated that (1) patients in group C (worsening without disease activity) were older and took longer to reach EDSS 3.0–4.0 than those in groups A, B and D ($p<0.05$); (2) patients in group D (worsening with disease activity) had a higher number of relapses before reaching EDSS 3.0–4.0 than those in group A (no worsening and no disease activity; $p<0.05$); (3) patients in groups B and D (with disease activity) were more likely to have Gd-enhancing lesions at study entry than those in groups A and C (without disease activity; $p<0.05$).

Predictors of increasing disability

Cox regression analysis indicated that, in the whole cohort, the risk of reaching the disability outcome was higher in patients older than 45 years (hazard ratio (HR) = 1.31, $p=0.04$) and in those who experienced more than six relapses before reaching an EDSS of 3.0–4.0 (HR = 1.32, $p=0.03$; Table 4). Consistently, when dividing the whole cohort into groups on the basis of the presence or absence of disease activity, we found that, in the group of patients with disease activity, experiencing more than six relapses before reaching an EDSS of 3.0–4.0 (HR = 1.53, $p=0.009$) was the only predictor of the subsequent confirmed increase in disability (Table 4); in the group of patients without disease activity, increasing disability was predicted only by an age older than 45 (HR=1.65, p=0.04). The Cox regression model provided similar results even after entering MS-specific treatment at study entry as a factor in the analysis.

Table 4. Cox proportional hazard regression models showing hazard ratio (HR), with their relative 95% confidence intervals (CIs), for reaching an EDSS score≥6.0 in the whole cohort of patients and in groups established on the basis of the presence or absence of disease activity.

Risk factors		Whole sample (n=542)			Patients with disease activity (n=334)			Patients without disease activity (n=208)		
		HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age	<37	1.00	–	–	–	–	–	1.00	–	–
	37–45	0.98	0.75–1.28	0.87				1.28	0.79–2.11	0.33
	>45	1.31	1.01–1.66	0.04				1.65	1.02–2.66	0.04
Relapses	<5	1.00	–	–	1.00	–	–	–	–	–
	5–6	0.95	0.73–1.24	0.72	1.17	0.83–1.64	0.38			
	>6	1.32	1.03–1.70	0.03	1.53	1.11–2.10	0.009			

EDSS: Expanded Disability Status Scale; CI: confidence interval.

Risk score of increasing disability

From the Cox regression models, we derived a composite risk score of confirmed increase in disability that included age and number of relapses as significant predictors of clinical evolution. The score was defined as follows:

1. Score=0, if the patient was ≤45 years and experienced ≤6 relapses before reaching an EDSS of 3.0–4.0;
2. Score=1, if the patient was >45 years or, alternatively, experienced >6 relapses before reaching an EDSS of 3.0–4.0;
3. Score=2, if the patient was >45 years and experienced >6 relapses before reaching an EDSS of 3.0–4.0.

In our cohort, 259 (48%) patients had a score of 0, 226 (41.7%) had a score of 1 and 57 (10%) had a score of 2. An increase in the risk score led to an increased probability of reaching the disability outcome (p=0.001 by the test for trend). Indeed, the probability of reaching the disability outcome was 56% for patients with a score of 0, 68% for patients with a score of 1 (HR=1.52, p=0.001) and 75% for patients with a score of 2 (HR=2.22, p<0.001; Figure 2).

Discussion

In this study, we focused on the clinical outcome of patients with relapsing-onset MS and moderate levels of disability to predict the individual clinical trajectories and identify the main factors driving disability evolution in the single case. We also offer an application of the revised MS phenotypes[1] in a contemporary, real-world cohort of MS patients, the majority of whom were on DMTs, given the ethical constraint of offering treatment to eligible patients in clinical practice. This is relevant to inform future trials on progressive MS that will need to consider the presence of DMTs in the enrolment criteria.[17]

To objectively assess disease evolution that reflects progression, we included patients with a baseline moderate level of disability, which, consistent with previous reports,[18] was attained in a median time of 12 years. The majority of our patients reached the milestone of EDSS 6.0 or more after a follow-up of 6 years, indicating that, as a group, disability evolution is an outcome to be expected in relapsing-onset MS patients[19] and confirming the time to the attainment of severe levels of disability that ranges from 14 to 28 years after onset.[18] Our results also quantify the proportion of patients who are stable or undergo confirmed increase in disability[1] and indicate that disease evolution occurs both in the presence and in the absence of clinical/MRI activity. While confirming the importance of early disease activity in subsequent disability evolution,[20] this finding also indicates that factors different from inflammatory activity play a relevant role in disability evolution.[8]

Our finding that disease activity predicts disability worsening extends previous evidence on the predictive value of relapses and MRI lesion volume changes during the first years of the disease for long-term disability[20,21] and for the development of secondary progression.[2] Although single relapses may have different impacts on disability evolution, depending on the characteristics of each relapse, the observation that persistent MRI activity (i.e. rate of lesion volume growth over time) in relapsing-onset MS identifies patients who will develop, or already have, a secondary progressive course[2] confirms our findings that disease activity leading to moderate levels of disability predicts a relapsing progressive clinical profile.

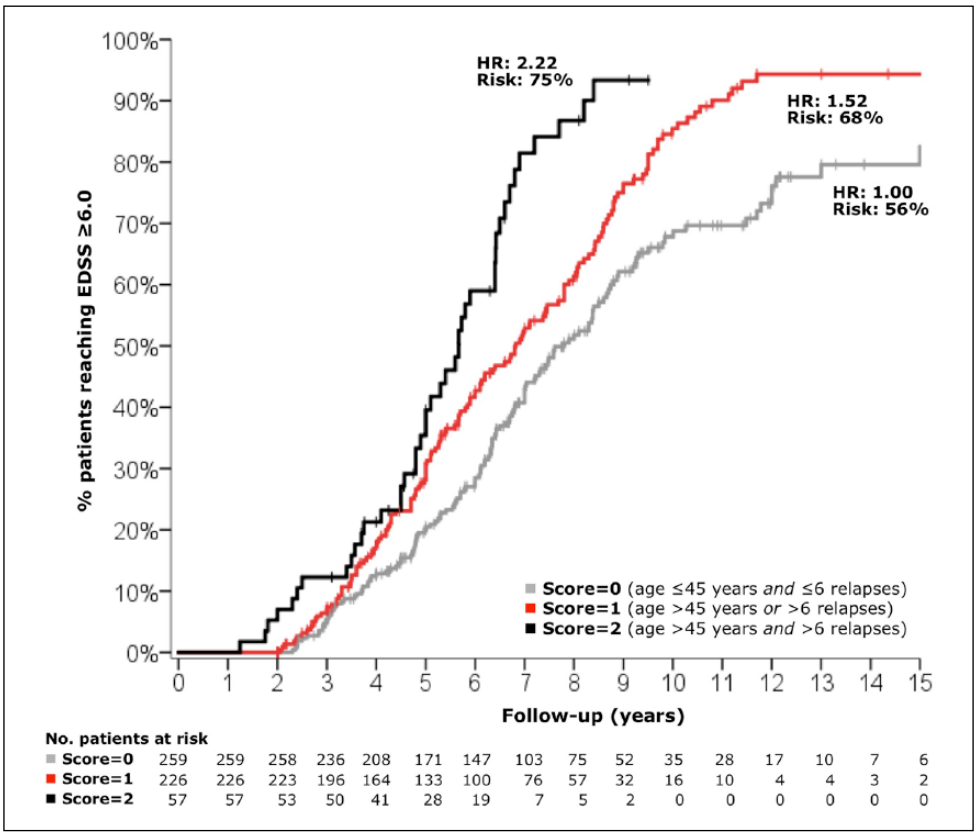

Figure 2. Kaplan–Meier curves for profiles of increasing disability in MS patients. A composite risk score is shown of increasing disability that includes age at the time of EDSS 3.0–4.0 and number of relapses before attaining EDSS 3.0–4.0 as significant predictors of clinical evolution. Risk indicates the proportion of patients who reached the disability outcome in each scoring group. Hazard ratio (HR) indicates the risk of reaching the disability outcome with respect to the reference group of patients with age ≤ 45 years and ≤6 relapses. An increase in the risk score leads to a significantly increased probability of reaching the disability outcome.

The relationship between early clinical/MRI activity and the later profile of disability development reflects the neuropathology of MS damage. Despite clinical heterogeneity in the course of MS, more inflammatory versus more degenerative evolutions can be identified by specific patterns of MS damage.[22] Also, at a given time point along the course of the disease, these patterns are homogeneous within the same patient, thus making the identification of individual disability profiles possible, as well as relevant for therapeutic implications.

Although in this study patients undergoing disability worsening in the presence of active disease were those with the highest number of relapses in the early phases of MS, the number of relapses preceding EDSS 3.0–4.0 did not differ significantly from that of patients with disease activity and no disability change or from that of patients who worsened in the absence of disease activity, suggesting the importance of other factors to the subsequent disease progression. Indeed, patients who increased their disability levels without disease activity were older and took longer to reach EDSS 3.0–4.0 than patients belonging to other groups, suggesting that age is an independent contributor to increasing disability. It is possible that DMTs may have masked the presence of disease activity in the proportion of patients that increased disability levels without showing disease activity.[23] However, age is a known prognosticator of MS.[24,25] Age at disability milestones is not substantially affected by the initial course of the disease, which raised the hypothesis of clinical phenotypes as an age-dependent manifestation.[19] Current age is the strongest predictor of Gd enhancement in the brain, with the average number of Gd-enhancing lesions decreasing significantly with increasing patient age independently of disease duration.[26] Age also impacts the reduction of relapse occurrence over time more than the disease duration[27] and a younger age at the beginning of DMT seems to be the most relevant factor associated with a higher treatment effect on disability progression in relapsing-onset patients.[5]

Several mechanisms may explain the role of aging in disability evolution. Normal aging affects immunity.[28] When premature, immunosenescence has been suggested as a factor predisposing to MS[28] and explaining the clinical specificity of late-onset disease.[29] Immunosenescence may also affect MS trajectory through changes in inflammatory activity[26] and increased susceptibility to neurodegenerative phenomena (e.g. mitochondrial dysfunction)[30] that could explain a disease profile characterised by increasing disability in the absence of clear inflammatory activity. Normal aging also modifies functional responses[31] and the brain tissue microarchitecture.[32] In MS, the widespread damage-related changes in structural connectivity and functional responses,[33,34] along with reduced repair capacity,[33] can interact with the aging processes, reducing further the brain reserve and predisposing the brain to other age-related pathological changes.[8] Neuropathological evidence suggests that normal aging can interact with MS inflammation. Indeed, the cortex of patients with progressive MS has a topographical distribution of neuronal retrograde degeneration similar to that present in aged controls.[8] Also, aged controls can show diffuse white matter damage with axonal transection (i.e. leukoaraiosis)[35] in the same periventricular regions as MS patients, suggesting that age-related pathology can contribute to white matter damage in MS and confirming our finding that the interaction of brain aging with early MS activity increases the risk of severe disability.

This work has some limitations that reflect its design as a real-world study. Although our patients underwent at least two neurological assessments per year, factors such as timing and the number of visits could differ between patients. To account for these differences, we conducted a time-to-event analysis that allowed us to right-censor the observation to the last available visit. The available MRI data included only the presence or absence of Gd-enhancing lesions. The information on new or enlarging T2, usually included in clinical trials, was inconsistent in the clinical reports of the patients and, when present, could be of limited reliability, given the possible differences in the scanning protocols between time points. Therefore, given our study design, we decided to use a more robust measure, that is, the presence or absence of activity as detected by Gd-enhancing lesions. Although patients were constantly treated since diagnosis, the use of DMTs before the inclusion in the study and during the study did not follow a specific protocol, as this was a real-life study, in which each patient received treatment according to the availability of specific DMTs and the clinical judgement of his or her disease trajectory. Of course, DMTs before, at the time of and after the attainment of EDSS 3.0–4.0 may have affected the presence of disease activity during the study and indirectly may have had an effect on EDSS increase. As this real-life study was not designed to investigate the impact of DMTs on subsequent disability increase, we could only test the relationship between DMTs at study entry, that is, at the point of EDSS 3.0–4.0, and disability increase. We were unable to demonstrate a predictive role of DMTs on disability increase, possibly due to differences among DMTs in the length of their follow-up, but we did show an association between high-efficacy treatments at the time of EDSS 3.0–4.0 and lower proportion of patients experiencing increasing disability during the study, supporting the hypothesis that inflammation can contribute to disability increase even in later stages of the disease.

Conclusion

The concept of MS as one disease with different clinical phenotypes[19] facilitates the clinical application of the revised classification of the disease courses.[1] However, the development of complex treatment strategies that aim at silencing MS demands an early recognition of disease trajectories in individual cases. This work helps meet this need and implies that (1) in patients with disease activity during the first years of MS, appropriate treatment interventions in the window of opportunity, that is, before reaching a level of moderate disability, can prevent or delay disability evolution; (2) as disease activity is an independent predictor of disability evolution, it should be treated regardless of the starting disability levels; (3) when a clear inflammatory target is missing or 'no evidence of disease activity' is achieved, age remains a crucial contributor to increasing disability. In these cases, more holistic approaches that include correct lifestyles and management of age-dependent comorbidities should be considered; (4) as age is an independent predictor of disability evolution, preserving brain resources through damage limitation and building reserve at an early stage of the disease can limit the subsequent development of disability; (5) quantifying the individual risk of disability attainment and describing the profile of clinical worsening can aid the development of personalised approaches to MS treatment.

Acknowledgements

Dr V Tomassini and Dr F Fanelli contributed to the conceptualisation of the study, data analysis and interpretation, and writing of the manuscript. Dr L Prosperini contributed to data analysis, interpretation

and manuscript revision for intellectual content. Dr P Cavalla contributed to data collection and manuscript revision for intellectual content. Prof. C Pozzilli contributed to conceptualisation of the study, interpretation of data and manuscript revision for intellectual content. Dr Maura Danni, MD (Institute of Neurology, Ospedali Riuniti, Marche Polytechnic University, Ancones, Italy) is a collaborator on this work through contribution to data collection. Dr V Tomassini, the principal author, and Prof. C Pozzilli, the last author, have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: L.P. has received consulting and lecture fees and travel grant from Biogen, Genzyme, Novartis and Teva. C.P. has received consulting, lecture fees and research funding and travel grant from Almirall, Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche and Teva. The other authors declare that they have nothing to disclose with respect to the subject matter of this manuscript.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

ORCID iDs

Valentina Tomassini https://orcid.org/0000-0002-7368-6280
Luca Prosperini https://orcid.org/0000-0003-3237-6267

References

1. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* 2014; 83: 278–286.
2. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: A 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008; 131: 808–817.
3. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis, a geographically based study 10: Relapses and long-term disability. *Brain* 2010; 133: 1914–1929.
4. Tomassini V, Paolillo A, Russo P, et al. Predictors of long-term clinical response to interferon beta therapy in relapsing multiple sclerosis. *J Neurol* 2006; 253: 287–293.
5. Signori A, Schiavetti I, Gallo F, et al. Subgroups of multiple sclerosis patients with larger treatment benefits: A meta-analysis of randomized trials. *Eur J Neurol* 2015; 22: 960–966.
6. Kappos L, Weinshenker B, Pozzilli C, et al. Interferon beta-1b in secondary progressive MS: A combined analysis of the two trials. *Neurology* 2004; 63: 1779–1787.
7. Steinman L and Zamvil SS. Beginning of the end of two-stage theory purporting that inflammation then degeneration explains pathogenesis of progressive multiple sclerosis. *Curr Opin Neurol* 2016; 29: 340–344.
8. Haider L, Zrzavy T, Hametner S, et al. The topograpy of demyelination and neurodegeneration in the multiple sclerosis brain. *Brain* 2016; 139: 807–815.
9. Vollmer TL, Sorensen PS, Selmaj K, et al. A randomized placebo-controlled phase III trial of oral laquinimod for multiple sclerosis. *J Neurol* 2014; 261: 773–783.
10. Confavreux C and Vukusic S. Age at disability milestones in multiple sclerosis. *Brain* 2006; 129: 595–605.
11. Harding KE, Wardle M, Moore P, et al. Modelling the natural history of primary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2015; 86: 13–19.
12. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald Criteria'. *Ann Neurol* 2005; 58: 840–846.
13. Leray E, Yaouanq J, Le Page E, et al. Evidence for a two-stage disability progression in multiple sclerosis. *Brain* 2010; 133: 1900–1913.
14. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. *Lancet* 1998; 352: 1491–1497.
15. Panitch H, Miller A, Paty D, et al. Interferon beta-1b in secondary progressive MS: Results from a 3-year controlled study. *Neurology* 2004; 63: 1788–1795.
16. Ebers GC, Heigenhauser L, Daumer M, et al. Disability as an outcome in MS clinical trials. *Neurology* 2008; 71: 624–631.
17. Ziemssen T, Hillert J and Butzkueven H. The importance of collecting structured clinical information on multiple sclerosis. *BMC Med* 2016; 14: 81.
18. Degenhardt A, Ramagopalan SV, Scalfari A, et al. Clinical prognostic factors in multiple sclerosis:

A natural history review. *Nat Rev Neurol* 2009; 5: 672–682.

19. Confavreux C and Vukusic S. Natural history of multiple sclerosis: A unifying concept. *Brain* 2006; 129: 606–616.
20. Binquet C, Quantin C, Le Teuff G, et al. The prognostic value of initial relapses on the evolution of disability in patients with relapsing-remitting multiple sclerosis. *Neuroepidemiology* 2006; 27: 45–54.
21. Sormani MP, Li DK, Bruzzi P, et al. Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis. *Neurology* 2011; 77: 1684–1690.
22. Lucchinetti C, Bruck W, Parisi J, et al. Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. *Ann Neurol* 2000; 47: 707–717.
23. Di Rezze S, Gupta S, Durastanti V, et al. An exploratory study on interferon beta dose effect in reducing size of enhancing lesions in multiple sclerosis. *Mult Scler* 2007; 13: 343–347.
24. Scalfari A, Neuhaus A, Daumer M, et al. Age and disability accumulation in multiple sclerosis. *Neurology* 2011; 77: 1246–1252.
25. Trojano M, Liguori M, Bosco Zimatore G, et al. Age-related disability in multiple sclerosis. *Ann Neurol* 2002; 51: 475–480.
26. Filippi M, Wolinsky JS, Sormani MP, et al. Enhancement frequency decreases with increasing age in relapsing-remitting multiple sclerosis. *Neurology* 2001; 56: 422–423.
27. Kalincik T, Vivek V, Jokubaitis V, et al. Sex as a determinant of relapse incidence and progressive course of multiple sclerosis. *Brain* 2013; 136: 3609–3617.
28. Ongradi J and Kovesdi V. Factors that may impact on immunosenescence: An appraisal. *Immun Ageing* 2010; 7: 7.
29. Martinelli V, Rodegher M, Moiola L, et al. Late onset multiple sclerosis: Clinical characteristics, prognostic factors and differential diagnosis. *Neurol Sci* 2004; 25(Suppl. 4): S350–S355.
30. Stahon KE, Bastian C, Griffith S, et al. Age-related changes in axonal and mitochondrial ultrastructure and function in white matter. *J Neurosci* 2016; 36: 9990–10001.
31. Chen PY, Chiou JM, Yang YF, et al. Heterogeneous aging effects on functional connectivity in different cortical regions: A resting-state functional MRI study using functional data analysis. *PLoS ONE* 2016; 11: e0162028.
32. Giorgio A, Santelli L, Tomassini V, et al. Age-related changes in grey and white matter structure throughout adulthood. *Neuroimage* 2010; 51: 943–951.
33. Franklin RJ, Zhao C and Sim FJ. Ageing and CNS remyelination. *Neuroreport* 2002; 13: 923–928.
34. Tomassini V, Matthews PM, Thompson AJ, et al. Neuroplasticity and functional recovery in multiple sclerosis. *Nat Rev Neurol* 2012; 8: 635–646.
35. Brown WR and Thore CR. Perivascular fibrosis in multiple sclerosis lesions. *Brain Pathol* 2011; 21: 355.