Published in final edited form as:

Mult Scler. 2013 February ; 19(2): 188–198. doi:10.1177/1352458512451510.

Onset of Progressive Phase is an Age Dependent Clinical Milestone in Multiple Sclerosis

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Abstract

Background—It is unclear if all patients with RRMS ultimately develop progressive MS. Onset of progressive disease course seems to be age- rather than disease duration dependent. Some forms of progressive MS (e.g. PPMS) are uncommon in population-based studies. Ascertainment of patients with PPMS from clinic-based populations can facilitate a powerful comparison of age-of-progression-onset between SPMS and PPMS but may introduce unclear biases.

Objective—To confirm that onset of progressive disease course is more relevant to patient's age than the presence or duration of a pre-progression relapsing disease course in MS.

Methods—We studied a population-based MS cohort (n=210, relapsing-remitting MS n=109, progressive MS n=101) and a clinic-based progressive MS cohort (n=754). Progressive course was classified as primary- (PPMS; n=322), single attack- (SAPMS; n=112) and secondary-progressive

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Contributions: O Kantarci, S Pittock, I Pirko, M Keegan, C Lucchinetti, B. Weinshenker, J Noseworthy, M Rodriguez performed clinical assessments. MS and Autoimmune Neurology Division clinical and research fellows (active and former), M Tutuncu, J Tang, N Abou Zeid, N Kale reviewed medical records, extracted data, conducted quality control evaluations and generated the database for the study. A. Siva, S. Pittock and M. Rodriguez established the original population-based MS cohort. O Kantarci, N Abou Zeid, J Tang, M Tutuncu, D Crusan and E Atkinson are responsible for study design, statistical design and data analyses. All authors have contributed to manuscript preparation and critique. O Kantarci has overseen all aspects of the study. O Kantarci takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures and Conflicts of Interest: The study was approved by the institutional review board of the Mayo Clinic and all patients included in the final study consented to the use of their medical record for research purposes. The authors report no conflict of interest

(SPMS; n=421). We studied demographics (chi2 or t-test), age-of-progression-onset (t-test) and time-to-EDSS6 (Kaplan-Meier analyses).

Results—Sex-ratio ($p=0.58$), age-of-progression-onset ($p=0.37$) and time-to-EDSS6 ($p=0.16$) did not differ between the cohorts. Progression had developed before age 75 in 99% of patients with known progressive disease course; 38% with RRMS did not develop progression by age 75. Age-of-progression-onset did not differ between SPMS (44.9 ± 9.6), SAPMS (45.5 ± 9.6) and PPMS (45.7 ± 10.8). In either cohort, only 2% of patients had reached EDSS6 before onset of progression.

Conclusions—Patients with RRMS do not inevitably develop progressive disease course. Onset of progression is more dependent on age than the presence or duration of a pre-progression symptomatic disease course. Moderate disability is sustained predominantly after the onset of a progressive disease course in MS.

Keywords

Multiple sclerosis; outcome measurement; progressive; relapsing remitting; EDSS; disability

Introduction

The course of multiple sclerosis (MS) is classified based on the temporal relationship between relapses from which patients typically experience partial or complete recovery and progression of irreversible central nervous system dysfunction.¹⁻⁴ A purely relapsing-remitting disease course (RRMS) is characterized by the absence of worsening neurological function outside of individual relapses. In this study, we focus on the onset of the progressive disease course in MS defined by the onset of insidiously worsening and irreversible neurological function, regardless of absence or presence of preceding relapses and that cannot be explained purely by a stepwise worsening associated with ongoing relapses.

A progressive disease course may start without preceding relapses (primary progressive MS - PPMS) or follow symptomatic relapses (bout-onset progressive MS - BOPMS). In the BOPMS groups, single-attack progressive MS (SAPMS) refers to progression following a clinically isolated syndrome (CIS) and secondary progressive MS (SPMS) refers to progression following RRMS.⁵

We seek to confirm that the onset of progressive MS may be more relevant to patient's age than the duration of a pre-progression relapsing disease course.^{2, 5-8} We hypothesize that the presence (BOPMS) or absence (PPMS) of a symptomatic relapsing-remitting period preceding onset of progressive disease course in MS may have no impact on the age-of-progression-onset. We ask the specific question if age-of-progression-onset is similar in the sub-groups of SPMS, SAPMS and PPMS. We also address several additional challenges that can confound the ascertainment and comparison of age-of-progression-onset in the sub-groups of SPMS, SAPMS and PPMS.

Population-based studies are the standard for determining age related milestones but may have limited power to study relatively uncommon forms of progressive MS (e.g. PPMS). Patients with progressive MS are commonly referred to tertiary-care clinics due to

challenges associated with their care enriching clinic-based-populations for the uncommon forms of progressive MS. However, mostly retrospective determination of age-of-progression-onset in clinic-based cohorts is likely more prone to recall bias than in prospectively followed population-based cohorts. Men have an older age-of-progression-onset and more severe MS than women.^{1, 9} Therefore, potential referral of more severe cases and potentially more men to clinic-based cohorts could lead to earlier age-of-progression-onset estimates than in population-based studies. To address the potential impact of recall and referral biases on age-of-progression-onset, we uniquely compare a clinic-based cohort of MS patients to a population-based cohort of MS patients ascertained in the same clinical practice for the sex-ratio, age-of-progression-onset and time-to-moderate-disability milestone of Expanded Disability Status Scale of six (EDSS6).^{5, 10}

Some patients with CIS or RRMS are not followed long enough to develop progressive disease course. The resulting censoring needs to be considered in studies focusing on age-of-progression-onset in BOPMS.⁶ This provides a challenge when comparing BOPMS patients to PPMS. By definition, all patients with PPMS have already reached the age milestone at the time of diagnosis. If some patients with CIS or RRMS will never develop progression, inclusion of these patients in longitudinal studies may lead to older age-of-progression-onset estimates for the BOPMS group than the PPMS group. In this study, we also seek to find out whether all patients with RRMS develop progressive MS in a longitudinally followed population-based cohort.

Methods

Study populations (Figure-1)

All patients were seen and followed at the Mayo Clinic Center for MS and CNS Demyelinating Diseases, a tertiary care provider for complicated referral patients with MS and a primary care provider for regional patients with MS.

We studied two cohorts fulfilling McDonald diagnostic criteria for MS^{11, 12}: a population-based MS cohort from Olmsted County, MN established in 1992¹³ and re-ascertained in 2002 (n= 221, age 18 years)^{14, 15}; and a clinic-based progressive MS cohort (n= 859, age 18 years) established from patients seen from 2003 through 2007, with observed progression of at least 1 year.

Definition of progression

We defined progression as insidious and irreversible worsening brain, brainstem-cerebellar and spinal cord syndromes most commonly characterized by progressive weakness, ataxia or bladder dysfunction of 1 year. We did not include patients with exclusive sensory progression due to subjectivity and variability in recording change in intensity of sensory symptoms. Typical of a standard clinical practice setting, the most detailed and rigorous historical documentation and clinical examination closest in time to progression onset was used to establish the date of onset of progression.

Disease course classification

Primary progressive MS (PPMS) is defined as progression without previous relapses. Single-attack progressive MS (SAPMS) is defined as progression following a clinically isolated syndrome.⁵ Secondary progressive MS (SPMS) is defined as progression following RRMS. Although separated for understanding potential impact of a single critical relapse before progression onset, SAPMS and SPMS are also grouped together as bout-onset progressive MS (BOPMS) when appropriate for the analyses.

Rather than as a separate relapsing-progressive MS category, ongoing relapses after onset of progression were considered as part of a continuum of the symptomatic (BOPMS) or subclinical (PPMS) relapsing phase as it evolved into progressive phase of MS.

The population-based cohort captured RRMS patients with or without conversion to SPMS despite a 20 year follow-up. As a tertiary care referral practice, the clinic-based cohort captured a population enriched for less common forms of progressive MS (PPMS and SAPMS) than SPMS.

Study variables and outcomes

We extracted the following variables: Sex; age at MS onset; age at progression onset; year of progression onset; age at sustained disability of clinically well-recognized and well-recorded milestone of EDSS6^{5, 10} or needing a cane to walk; age at last relapse; occurrence of pre-progression and post-progression relapses. We studied the following outcomes: time from onset of MS to onset of progression, age-of-progression-onset and time from progression onset to EDSS6 (time-to-EDSS6).

Data extraction and validation (Figure-1)

In the population-based cohort with prospective follow-ups in our center, two neurologists with subspecialty training in MS (JT, MT) independently reviewed all neurologic and non-neurologic records and agreed on date of progression and date of EDSS6 in each case.

Two additional neurologists with MS subspecialty training (NA, NK) reviewed all neurologic and non-neurologic records for the clinic-based cohort. Year of progression onset was identical according to the two reviewers in 26 of the first 30 reviewed patients. The year of attaining EDSS6 matched in 26 of 28 patients (2 of 30 had not reached EDSS6 in this group). In the cases where records at different time points indicated different dates for progression onset or EDSS6, decision was made to use the earliest record closest to the event date. Any final discrepancies were arbitrated by the principal investigator (OK). Despite consensus that the course was progressive, we could not clarify presence or absence of pre-progression relapses in 19 (2.5%) patients from the clinic-based cohort who were excluded from the final analyses (Figure-1).

Data analyses

To assess for potential impact of referral and recall biases on age-of-progression-onset in the largely retrospective tertiary care clinic-population, we compared sex-ratio, age at MS onset, age-of-progression-onset and time-to-EDSS6 in the two cohorts.

Demographic and clinical features in different models were compared by χ^2 or t-tests as appropriate. Kaplan-Meier analysis was used to account for censoring, age- or time-scaled outcomes (i.e. where RRMS patients that are yet-to-progress are included in the analyses). Mean values with standard deviations from the mean were provided when appropriate (i.e. where all patients included in the analyses have reached the outcome).

Results

To prevent double counting of patients in the final analyses, patients who overlapped the two cohorts were included in the population-based cohort (Figure-1). Analyses were performed with 109 patients who still had RRMS without clinical progression (mean follow-up $\pm$ SD: 22.4 ± 11.9 years; 71% ≥ 15 and 40% ≥ 25 years follow-up), 101 patients with progressive MS (80 SPMS, 6 SAPMS, 15 PPMS) from the population-based cohort and 754 patients with progressive MS (341 SPMS, 106 SAPMS, 307 PPMS) from the clinic-based cohort (Figure-1).

To account for regional patient-referral patterns that could impact age at progression onset, the clinic-based cohort was further sub-grouped to include only the patients from the states within latitudes $40^\circ - 50^\circ$ surrounding Olmsted County (MN, ND, SD, NE, WI, IA, MI - upper peninsula) (Table-1). There was no difference in regional vs non-regional referrals in any of the outcomes that were analyzed; therefore they were grouped for further analyses.

1) Do sex-ratio, age-of-progression-onset and time-to-EDSS6 differ between clinic-based and population-based MS patients?

Table-1 shows the demographic aspects of patients with progressive MS from the population-based cohort compared to the clinic-based cohort. Analyses were done both by including and excluding PPMS patients. Sex ratio did not differ between populations (Table-1).

MS onset was 3.5 years older for patients with BOPMS in the clinic-based cohort compared to the population-based cohort (mean $\pm$ SD: 33.5 ± 9.6 years versus 29.9 ± 8.8 years; $p=0.001$) (Table-1). Age-of-progression-onset ($p=0.37$) did not differ between clinic- and population-based cohorts (Table-1). Time-to-EDSS6 did not differ between clinic- and population-based cohorts, regardless of inclusion ($p=0.16$) or exclusion ($p=0.86$) of PPMS (Figure-2).

Despite a long follow-up (mean $\pm$ SD: 22.8 ± 11.8 years), only 2 of 109 (1.8%) patients in the RRMS group without secondary progression reached EDSS6. Similarly, 2 of 85 (2.4%) patients from the population-based cohort and 7 of 447 (1.6%) patients from the clinic-based cohort with established BOPMS reached EDSS6 before progression (Table-1).

2) Do all patients with RRMS ultimately progress?

Four models were applied to the population-based cohort using Kaplan-Meier estimates of time-to-progression and age-of-progression-onset (Figure-3). Model-1 includes the patients with established SPMS only. Model-2 includes patients with established SPMS and the 109 patients still with RRMS as of their last follow-up; 9 patients who died and 100 patients who

had their last follow-up before the year 2010 were excluded. To consider extreme estimates for the excluded patients, Model-3 (upper limit) assumed that all RRMS patients develop SPMS within a year from their last follow-up or death, whereas Model-4 (lower limit) assumed that all RRMS patients remain RRMS as of 2010.

Within 35 years of MS onset, 94% of patients with established SPMS (Model-1) had already developed progression. When patients with RRMS as of their last follow-up were included (Model-2), 45% of patients had not yet developed progression by 35 years post-MS onset (Models-3 and 4 suggested a range of 13% to 52%).

At age 75, 99% of patients with established SPMS (Model-1) had already developed progression. When patients with RRMS as of their last follow-up were included (Model-2), 38% of patients had not yet developed progression at age 75 (Models-3 and 4 suggested a range of 3% to 42%).

3) Does the presence (BOPMS) or absence (PPMS) of a pre-progression symptomatic relapsing-remitting phase impact age-of-progression-onset?

Our hypothesis required comparison of SPMS and SAPMS with PPMS for age-of-progression-onset. Studying the pre-progression disease course in PPMS is akin to ascertaining all radiologically isolated syndrome (RIS) patients in the population¹⁶⁻¹⁹ and is not practical. Since about one third of RRMS patients may also never develop progressive disease course it was more appropriate to exclude yet-to-progress RRMS patients for a head-to-head comparison of age-at-progression-onset between BOPMS and PPMS.

Given the similar sex ratio, age-of-progression-onset, and ratio of attainment of EDSS6 before progression between the two cohorts, patients with progressive MS from each cohort were combined. Distribution of age at first clinical symptoms of MS and age at progression onset stratified by disease course (PPMS, SAPMS, SPMS) revealed that age at MS onset was earlier for patients with SPMS (31.8 ± 9.3) versus SAPMS (37.4 ± 9.4) versus PPMS (45.7 ± 10.8) ($P < 0.001$) (Figure-4). However, age-of-progression-onset did not differ by disease course (SPMS: 44.9 ± 9.6 , SAPMS: 45.5 ± 9.6 , PPMS: 45.7 ± 10.8 , $p = 0.23$). We also found that while the proportion of patients who experienced relapses after progression onset differed by disease course (SPMS 27.3%, SAPMS 12.3%, PPMS 0.3%; $p < 0.0001$), age at last relapse after progression did not differ by disease course (SPMS 48.1 ± 9.5 , SAPMS 49.6 ± 8.8 , PPMS 47.8 ± 10.2 ; $p > 0.05$).

Discussion

We made several specific observations that pertain to the onset of progressive disease course in MS. About one third of RRMS patients may never develop a progressive disease course. Age-of-progression-onset is similar between BOPMS and PPMS. Age-of-progression-onset is similar between a population-based cohort and a clinic-based cohort ascertained within the same clinical practice setting. Sustained moderate disability seems to be attained predominantly after the onset of a progressive disease course in MS. We discuss these findings individually below.

Switching from relapses to progression in MS is an age-dependent process independent of pre-progression disease course or disease duration

We novelly show that almost all patients with MS develop progressive disease course before age 75 (or by 35 years post-MS onset), while 38% of patients with RRMS are predicted not to develop progression by age 75. Identifying the intriguing underlying biology and predictors of non-progression can help design novel therapeutics to prevent progression, improve patient counseling and help better stratify patients for clinical trials.

Age of progression onset was independent of pre-progression clinical relapse-based classification of PPMS, SAPMS or SPMS in the current study, as previously reported.^{2, 5} We confirm that onset of progression in MS is age- rather than pre-progression disease duration dependent.^{7,8} PPMS occurs only infrequently in children^{20, 21}, further supporting that progression is an age-dependent process.

In the current study, ongoing relapses after progression onset were more common in SPMS than in SAPMS or PPMS, mirroring the frequency of pre-progression clinical relapses. However, a novel finding is that the age at last relapse was similar regardless of disease course classification of PPMS, SAPMS or SPMS. The end of the relapsing phase like the onset of progressive phase in MS also seems to be an age rather than disease duration dependent process.

Recent imaging studies suggest that myelination of the compact white matter ends by the 4th decade followed by a slow degeneration in the white matter tracts in the following decades.^{22, 23} Continued white matter tract repair (myelin and axons) may compensate for degeneration in previously damaged areas of the CNS until the end of 4th decade. An advancing degenerative phenotype afterwards is possibly reflected by the clinical progression surfacing in the 5th decade as in our study.

The relapsing phase of MS can manifest as symptomatic relapses (i.e. RRMS) or subclinical lesions (i.e. radiologically isolated syndrome - RIS)¹⁶⁻¹⁹. The current diagnostic criteria for MS utilize subclinical lesions by MRI to establish dissemination in time and space during the first encounter with the patient that already had a clinical relapse or slowly progressive disease course.²⁴ Patients with PPMS may have an “established” lesion load on MRI at onset of progression indistinguishable from that in patients with SPMS. SPMS follows RRMS clinically while PPMS follows RIS in a similar but subclinical continuum.^{25, 26} In patients matched for the total number of brain and spinal cord lesions, SPMS and PPMS differ by the presence of previous and ongoing inflammatory demyelination and recovery potential of individual lesions but share a similar spectrum of slowly expanding demyelination and axonal injury.²⁷ Our study further contributes to the unifying clinical scheme that SPMS, SAPMS and PPMS likely share a common neurodegenerative mechanism of progression but differ by the extent to which inflammatory-demyelinating activity manifests as preceding clinical relapse(s).^{2, 5}

Recruitment of progressive MS patients to studies through referral practices does not introduce any significant additional biases than expected in population-based cohorts that could impact age-of-progression onset determination

While the population-based studies are the standard for studies like ours we had a paucity of SAPMS and PPMS patients when compared to SPMS in our population-based cohort. Therefore we studied an additional clinic-based-cohort established from our practice. The higher incidence of SAPMS (14%) and PPMS (41%) in the clinic-based cohort than in our population-based cohort (6% and 15%) and another population-based cohort ⁵ confirms that patients with less common forms of progressive MS than SPMS are over-represented among patients referred to tertiary care practices.

Inclusion of clinic-based-cohort of patients could have potentially introduced additional recall and referral biases to our analyses. To address this we compared two populations to each other. We found that when ascertainment and follow-up are conducted in a relatively uniform clinical practice setting, age-of-progression-onset and attaining the disability milestone of EDSS6 in the retrospective tertiary clinic-based cohort were similar to that of the prospective population-based cohort. We noted that the age-of-progression-onset was one year younger in the population-based cohort, a small difference that did not reach statistical significance within the power limitations of our study.

Age at MS onset in RRMS did not differ between those with and those without secondary progression in the population-based cohort but was older in the clinic-based cohort compared to the population-based cohort. This suggested a potential recall bias for age at MS onset in the largely retrospective clinic-based cohort. However, our primary outcome measure of age-of-progression-onset did not differ significantly between clinic-based and population-based cohorts or between regional or non-regional referrals. Therefore, age-of-progression-onset, a more recent and potentially more life-changing event than the first MS event did not appear to be as prone to a potential recall bias as the age at MS onset.

Men are generally accepted to have older age at onset of MS and more severe disease than women ^{1,9} but men were only slightly over-represented in our clinic-based practice which did not reach statistical significance within the power limitations of our study. However it is possible that the non-significant one year delay in age-of-progression-onset in the clinic-based cohort is due to a slightly higher representation of men in this population. Time-to-EDSS6 did not differ between clinic-based and the population-based cohorts of progressive MS, either. We confidently concluded that our results regarding age-of-progression-onset therefore were unlikely to be confounded by a major recall or referral bias specific to the clinic-based cohort.

Commonly used disease modifying medications (DMDs) in MS do not seem to impact progressive disease course after it is established except for some benefit on preventing additional disability burden that may ensue because of superimposed relapses. ²⁸ It is however unclear if DMDs can delay onset of progression in the first place in BOPMS patients. Since our study is not planned as a prevention trial and PPMS patients naturally did not have pre-progression DMD use there was no way to properly control for this factor in our analyses when comparing age-of-progression-onset between BOPMS and PPMS.

EDSS6 is a disability milestone that is reached predominantly after the onset of progressive disease course in MS

EDSS6 and higher levels of the scale are biased towards the longest corticospinal tracts and naturally could reflect the impact of progression-related disability.^{5, 10} Progressive disease course has been the strongest determinant of sustained disability measured by EDSS.^{1-4, 9, 29-31} Attainment of the disability milestone of sustained EDSS4 is inevitably followed by further worsening of disability.³² Disability progression can result from relapses that partially recover or a progressive disease course or both. The contribution of relapses on disability progression decreases in time.³³ Individual relapses affecting the efferent motor pathways are less likely than relapses affecting afferent pathways to lead to chronic impairment in patients with MS.³⁴

While almost all SPMS cases develop progressive phase of MS when their disability is EDSS6 or less⁵ it was not known what percentage of patients with RRMS without progression can reach sustained EDSS6. A recent clinic-based study found that only 0.3% of individual relapses resulted in a sustained disability of EDSS6 or greater.³⁵ In our study 2% of patients without progression reached sustained EDSS6 representing the population-based frequency of “malignant relapsing-remitting” cases of MS.³⁶ In contrast, regardless of the cohort, 98% of patients who developed progression reached EDSS6 after progression onset. We conclude that EDSS6 is a disability milestone that is reached predominantly after the onset of progressive disease course in MS.

Interestingly, as in the case for developing progressive disease course in MS the speed of reaching the EDSS milestones seems to be age- rather than pre-progression disease course-dependent.^{32, 37, 38} This intricate relationship between age of the patient, onset of progressive disease course and evolution of disability milestones needs to be accounted for in clinical trials and epidemiology studies in MS.

Acknowledgments

The study has been supported by the Mayo Clinic Rochester Department of Neurology and a pilot grant from the National Multiple Sclerosis Society.

N Abou Zeid, C Atkinson, D Crusan, N Kale, J Noseworthy, A Siva, J Tang and M Tutuncu have no grant support. O Kantarci receives support from the Hilton Foundation and the European Regional Development Fund - Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123). BM Keegan receives support from NINDS (U01 NS 45719) and Biogen Idec., (Protocol Number 101JC402). C Lucchinetti receives support from NINDS (R01 NS 49577-6 and 2P50NS038667-11), NIH (UL1 RR 24150-2) and the Guthy-Jackson Charitable Foundation. I Pirko is supported by NINDS (R01 NS058698-01A2, R01 NS 58698, R01 NS 60881 and R01 NS060881-01A209) and the Guthy-Jackson Charitable Foundation. S Pittock receives support from NINDS (R01 NS 65829), the Guthy-Jackson Charitable Foundation and Alexion Pharmaceuticals, Inc. M Rodriguez receives support from the NIH (R01 GM092993, R01 NS024180, R01 NS032129, R01 NS048357 and R21 NS073684), the NIH CTSA (Center for Translational Science Activities - HIPFA) through grant number UL1 RR024150 from the National Center for Research Resources (NCRR), the National Multiple Sclerosis Society (CA 1060A11), as well as the Applebaum, Hilton and Peterson Foundations, the Minnesota Partnership Award for Biotechnology and Medical Genomics and the European Regional Development Fund - Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123). B Weinshenker receives support from the Guthy-Jackson Charitable Foundation.

References

1. Kantarci OH, Weinshenker BG. Natural history of multiple sclerosis. *Neurologic Clinics*. 2005; 23(1):17–38. [PubMed: 15661086]

2. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain*. 2006; 129(Pt 3):606–16. [PubMed: 16415308]
3. Lublin FD, Reingold SC. 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*. 1996; 46(4):907–11. [PubMed: 8780061]
4. Wolinsky JS. The diagnosis of primary progressive multiple sclerosis. *Journal of the neurological sciences*. 2003; 206(2):145–52. [PubMed: 12559502]
5. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. *Brain*. 2006; 129(Pt 3):584–94. [PubMed: 16401620]
6. Tremlett H, Zhao Y, Devonshire V. Natural history comparisons of primary and secondary progressive multiple sclerosis reveals differences and similarities. *J Neurol*. 2009; 256(3):374–81. [PubMed: 19308306]
7. Koch M, Mostert J, Heersema D, De Keyser J. Progression in multiple sclerosis: further evidence of an age dependent process. *J Neurol Sci*. 2007; 255(1-2):35–41. [PubMed: 17331540]
8. Scalfari A, Neuhaus A, Daumer M, Ebers GC, Muraro PA. Age and disability accumulation in multiple sclerosis. *Neurology*. 77(13):1246–52. [PubMed: 21917763]
9. Kantarci O, Siva A, Eraksoy M, et al. Survival and predictors of disability in Turkish MS patients. Turkish Multiple Sclerosis Study Group (TUMSSG). *Neurology*. 1998; 51(3):765–72. [PubMed: 9748024]
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983; 33(11):1444–52. [PubMed: 6685237]
11. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001; 50(1):121–7. [PubMed: 11456302]
12. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. *Annals of Neurology*. 2005; 58(6):840–6. see comment. [PubMed: 16283615]
13. Rodriguez M, Siva A, Ward J, Stolp-Smith K, O'Brien P, Kurland L. Impairment, disability, and handicap in multiple sclerosis: a population-based study in Olmsted County, Minnesota. *Neurology*. 1994; 44(1):28–33. [PubMed: 8290086]
14. Pittock SJ, Mayr WT, McClelland RL, et al. Change in MS-related disability in a population-based cohort: a 10-year follow-up study. *Neurology*. 2004; 62(1):51–9. [PubMed: 14718697]
15. Kantarci OH, Hebrink DD, Achenbach SJ, et al. Association of APOE polymorphisms with disease severity in MS is limited to women. *Neurology*. 2004; 62(5):811–4. see comment. [PubMed: 15007140]
16. McDonnell GV, Cabrera-Gomez J, Calne DB, Li DK, Oger J. Clinical presentation of primary progressive multiple sclerosis 10 years after the incidental finding of typical magnetic resonance imaging brain lesions: the subclinical stage of primary progressive multiple sclerosis may last 10 years. *Mult Scler*. 2003; 9(2):204–9. [PubMed: 12708816]
17. Siva A, Saip S, Altintas A, Jacob A, Keegan BM, Kantarci OH. Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. *Mult Scler*. 2009; 15(8):918–27. [PubMed: 19667020]
18. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis. The radiologically isolated syndrome. *Neurology*. 2008
19. Lebrun C, Bensa C, Debouverie M, et al. Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile. *J Neurol Neurosurg Psychiatry*. 2008; 79(2):195–8. [PubMed: 18202208]
20. Yeh EA, Chitnis T, Krupp L, et al. Pediatric multiple sclerosis. *Nature reviews*. 2009; 5(11):621–31.
21. Renoux C, Vukusic S, Mikaeloff Y, et al. Natural history of multiple sclerosis with childhood onset. *N Engl J Med*. 2007; 356(25):2603–13. [PubMed: 17582070]

22. Westlye LT, Walhovd KB, Dale AM, et al. Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. *Cereb Cortex*. 20(9):2055–68. [PubMed: 20032062]
23. Hasan KM, Kamali A, Abid H, Kramer LA, Fletcher JM, Ewing-Cobbs L. Quantification of the spatiotemporal microstructural organization of the human brain association, projection and commissural pathways across the lifespan using diffusion tensor tractography. *Brain structure & function*. 214(4):361–73. [PubMed: 20127357]
24. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011; 69(2):292–302. [PubMed: 21387374]
25. Thompson AJ, Kermode AG, Wicks D, et al. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Ann Neurol*. 1991; 29(1):53–62. [PubMed: 1996879]
26. Thompson AJ, Polman CH, Miller DH, et al. Primary progressive multiple sclerosis. *Brain*. 1997; 120(Pt 6):1085–96. [PubMed: 9217691]
27. Bramow S, Frischer JM, Lassmann H, et al. Demyelination versus remyelination in progressive multiple sclerosis. *Brain*. 2010; 133(10):2983–98. [PubMed: 20855416]
28. 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(10):1779–87. [PubMed: 15557490]
29. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain*. 1989; 112(Pt 1):133–46. [PubMed: 2917275]
30. Confavreux C, Aimard G, Devic M. Course and prognosis of multiple sclerosis assessed by the computerized data processing of 349 patients. *Brain*. 1980; 103(2):281–300. [PubMed: 7397479]
31. Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. *Brain*. 1993; 116(Pt 1):117–34. [PubMed: 8453453]
32. Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. *Brain*. 2006; 129(Pt 3):595–605. [PubMed: 16415309]
33. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y. Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology*. 2009; 73(20):1616–23. [PubMed: 19890070]
34. Benetto L, Burrow J, Sakai H, Cobby J, Robertson NP, Scolding N. The relationship between relapse, impairment and disability in multiple sclerosis. *Mult Scler*. 17(10):1218–24. [PubMed: 21622592]
35. Bejaoui K, Rolak LA. What is the risk of permanent disability from a multiple sclerosis relapse? *Neurology*. 74(11):900–2. [PubMed: 20231665]
36. Gholipour T, Healy B, Baruch NF, Weiner HL, Chitnis T. Demographic and clinical characteristics of malignant multiple sclerosis. *Neurology*. 76(23):1996–2001. [PubMed: 21646626]
37. Trojano M, Liguori M, Bosco Zimatore G, et al. Age-related disability in multiple sclerosis. *Ann Neurol*. 2002; 51(4):475–80. [PubMed: 11921053]
38. Confavreux C, Vukusic S. Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. *Clin Neurol Neurosurg*. 2006; 108(3):327–32. [PubMed: 16413961]

Figure-1.

Study design, patient populations and final disease course classification.

RRMS = relapsing remitting MS, PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, SAPMS = single attack progressive multiple sclerosis.

* We included the 28 patients [SPMS (n=22), SAPMS (n=5), PPMS (n=1)] overlapping between the two cohorts only in the population-based cohort.

† "Progression" refers to insidious and irreversible worsening brain, brainstem-cerebellar and spinal cord syndromes most commonly characterized by progressive weakness, ataxia or bladder dysfunction of 1 year

‡ The term "No progression" refers to patients whose disability derives from incomplete recovery from ongoing relapses alone rather than from insidious accumulation of neurological deficits.

Figure-2.

Kaplan-Meier estimates (with life-tables) of time to moderate disability after progression onset are shown for the population-based and clinic-based MS cohorts. All progressive MS patients (a) and bout-onset progressive MS patients (b) are shown separately. “Progression” refers to insidious and irreversible worsening brain, brainstem-cerebellar and spinal cord syndromes most commonly characterized by progressive weakness, ataxia or bladder dysfunction of 1 year. In the population-based cohort from the Olmsted County, MN (n=210), patients with RRMS (n=109) and patients where age at onset of progression was

not clear (n=1 SAPMS) were excluded. In the clinic-based referral patients (n=773), patients where pre-progression disease course was not clear (n=19) were excluded. This figure illustrates that for patients with progressive MS, there is no referral bias due to more severe disease after progression onset in the clinic-based cohort compared to the population-based cohort.

PPMS = primary progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, SAPMS = single attack progressive multiple sclerosis, EDSS6 = expanded disability status scale of 6

Figure-3.

Kaplan-Meier estimates (with life-tables) of time to progression (a) and age at progression (b) are shown in the longitudinally followed population-based cohort of patients with MS older than age 18 in Olmsted County, MN (n=210). Patients whose date of onset could not be precisely defined [SPMS (n=4), SAPMS (n=6) and PPMS (n=15)] are excluded from the analyses. Model-1 assumes that some patients with MS will never develop progression and therefore includes only patients with already established SPMS (n=80). Model-2 assumes that patients with MS may at one point develop progression (censored data) and therefore

includes patients still with RRMS (n=105) as of their last follow-up together with patients with already established SPMS. Model-3 assumes that all RRMS patients with censored data due to death or last follow-up before 2010 would have converted to SPMS within one year of their last follow-up establishing the upper extreme limit for model-2. Model-4 assumes that all of the RRMS patients who are deceased or lost to follow-up remain RRMS as of 2010 establishing the lower-extreme limit for Model-2. These models predict that that not all patients with MS develop progression despite sufficient follow-up. “Progression” refers to insidious and irreversible worsening brain, brainstem-cerebellar and spinal cord syndromes most commonly characterized by progressive weakness, ataxia or bladder dysfunction of 1 year

PPMS = primary progressive multiple sclerosis, SAPMS = single attack progressive multiple sclerosis, SPMS = secondary progressive multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis

Figure-4.

Age at developing first clinical symptoms MS (a) and age at reaching progression (b) curves, along with life-table analyses and mean ($\pm$ standard deviation) values are shown for SPMS versus SAPMS versus PPMS. All patients with progressive MS from both cohorts are included in the analyses. In the population-based cohort from the Olmsted County, MN ($n=210$), we excluded patients with RRMS ($n=109$) and patients whose age at onset of progression was not clear ($n=1$ SAPMS). In the clinic-based referral patients ($n=773$), we excluded patients where presence or absence of pre-progression relapses were not well

documented (n=19). Age at progression does not differ according to whether there were preceding relapses, but age at onset of MS, defined either by the first relapse (SPMS and SAPMS) or progression onset (PPMS), is significantly earlier for SPMS compared to SAPMS compared to PPMS. “Progression” refers to insidious and irreversible worsening brain, brainstem-cerebellar and spinal cord syndromes most commonly characterized by progressive weakness, ataxia or bladder dysfunction of 1 year
SPMS = secondary progressive multiple sclerosis, SAPMS = single-attack progressive multiple sclerosis, PPMS = primary-progressive multiple sclerosis

Table – 1
Comparison of population-based cohort of MS with clinic-based cohorts of MS

	Population-based *		Clinic-based *	
	All **	p	Regional ***	p
All progressive MS (SPMS + SAPMS + PPMS) (N)	100	754	441	
	Female / Male (N) †		277 / 164	0.43
	Age (years) at Progression Onset (<i>mean ± SD</i>) ††	43.7 ± 10.9	45.3 ± 10.1	0.16
Bout-onset progressive MS (SPMS + SAPMS) (N)	85	447	270	
	Female / Male (N) †	60 / 25	190 / 80	0.97
	Age (years) at Progression Onset (<i>mean ± SD</i>) ††	44.1 ± 10.7	45.1 ± 9.4	0.43
	Age (years) at First Relapse (<i>mean ± SD</i>) ††	29.9 ± 8.8	33.2 ± 9.4	0.004
	Time (years) to Progression (<i>mean ± SD</i>) ††	14.2 ± 11.1	11.9 ± 8.0	0.033
	Reaching EDSS6 before progression (%) †	2 (2.4)	4 (1.5)	0.59

PPMS = primary progressive MS, SPMS = secondary progressive MS, SAPMS = single attack progressive MS, EDSS6 = expanded disability status scale of 6

* In the population-based cohort from the Olmsted County, MN (n=210), patients with RRMS (n=109) and patients where age at onset of progression was not clear (n=1 SAPMS) were excluded. In the clinic-based referral patients (n=773), patients where pre-progression disease course was not clear (n=19) were excluded.

** All clinic-based referral patients except from the Olmsted County, MN

*** Regional clinic-based referral patients from the states within latitudes 40° - 50° surrounding Olmsted County (MN, ND, SD, NE, WI, IA, MI - upper peninsula)

† Chi² statistics;

†† Student T test statistics