New perspectives in the natural history of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) has entered an era of immunomodulatory drug treatment, the impact of which on long-term disease progression remains controversial. The increasing use of these therapies has intensified our need to understand the true natural history of MS. The MS community is poised to establish whether the immunomodulatory drugs exhibit long-term benefits, with a suitable untreated natural history cohort likely the most practical and ethical comparator group. Thus, a thorough understanding of the natural history of MS is fundamental. In this review, we highlight recent advances in MS natural history over the last 5 years, with a focus on long-term population-based cohorts and factors associated with disease progression. Survival in MS has increased and longer times to irreversible disability have been reported in contemporary studies, indicating a slower accumulation of disability. Wide variation in the MS disease trajectory is evident within and between natural history studies, reflecting both methodologic considerations related to data collection and heterogeneity of disease activity. Recent publications have indicated that a younger age at disease onset is no longer indicative of a favorable outcome and further evidence supports the dissociation between relapses and long-term disability, although windows of opportunity may exist for some patients. We are now perhaps faced with our last chance to examine the true natural history of MS, so whether the reader is a practicing physician, health care provider, or researcher, or engaged in the pharmaceutical industry or in clinical trial design, recent advances in our understanding of the natural history of MS are of key significance. Neurology® 2010;74:2004 –2015

GLOSSARY

DSS – Disability Status Scale; EDSS – Expanded Disability Status Scale; MS – multiple sclerosis.

Multiple sclerosis (MS) is typified by inflammation and chronic degeneration of the CNS. Demyelination and axonal destruction occur, making MS the most common cause of neurologic disability in young adults in the Western world. Observations of the natural history of MS date back to case reports from the 15th and 16th centuries, often in the form of autobiographical diaries. More comprehensive cohort studies appeared in the 1940s, and modern epidemiologic data collection has allowed interstudy comparisons using standardized outcome measures (the [Expanded] Disability Status Scale), internationally accepted disease course classification (relapsing-remitting, secondary-progressive, and primary-progressive1), and common statistical approaches (survival analysis).

In this review, we highlight recent advances in MS natural history (the last 5 years) in the context of previous knowledge (comprehensively reviewed elsewhere2). We focus on long-term population-based cohorts and factors associated with disease progression.

VALUE AND APPLICATION OF MS NATURAL HISTORY STUDIES MS natural history studies typically follow cohorts of patients with MS not treated prophylactically with any disease-modifying drugs over extended periods of time. As MS is a chronic disease with an extended trajectory, long-term follow-up is considered optimal. This also allows differentiation of short-term deterioration from long-term deficits.
Long-term natural history studies have numerous applications in MS. Based on the patient/physician perspective, findings from natural history studies guide advice regarding prognosis and allow informed decisions about initiation or cessation of immunomodulatory drug treatment. For example, knowledge that the MS natural history can often be favorable has led groups, such as the Mayo Clinic, to advocate not treating every eligible patient with MS with an immunomodulatory drug. Determining whether immunomodulatory drugs contribute meaningfully to slowing the long-term disease progression in MS requires an untreated patient comparator group with a long-term follow-up; probably our only current ethical means of finding such a group is through existing natural history cohorts/databases. Clinical trialists can benefit from natural history–derived estimates, facilitating study design, from sample size and power calculations to selecting valid, clinically relevant endpoints achievable in the time available and even determining which patient population to target. From the policy, health, and resource planner’s perspective, projections of disability outcomes in populations can help table effective health care management, ensuring availability of adequate provisions to cover drug costs and the impact of MS on society.

CURRENT UNDERSTANDING AND RECENT ADVANCES IN MS NATURAL HISTORY

Up until the early 2000s, MS was generally viewed as a fairly rapidly progressing disease, with 50% of patients reported as needing a cane, crutch, or brace to walk 100 m within 15 to 20 years from disease onset (figure 1).

MS prognosis: Is disease progression slowing? Figures 1 and 2 show major findings from the main longitudinal natural history studies published over the last decade.

MS is a notoriously variable disease; however, more recent natural history studies, using comparable survival analysis techniques, report longer times to disability milestones. Ranking studies by date order (oldest first, see figure 1), the median times to requiring a cane to walk (Expanded Disability Status Scale [EDSS] 6/Disability Status Scale [DSS] 6/European Database for Multiple Sclerosis impairment scale 6) ranged from 15 to 32 years. However, there is heterogeneity between natural history studies in terms of design, data collection, definition of outcomes, and analysis (figure 1 and table 1). Use of different definitions to assign time to cane (some requiring a confirmed and sustained attainment of DSS/EDSS 6, others not) and retrospective vs prospective assignment of scores compound the already well-documented interrater variability of the EDSS/DSS. The proposed temporal changes in gender ratio and MS incidence could also affect findings between studies, as an altered profile of the MS population could lead to apparent changes in the natural history. If more women and hence proportionally more relapsing–remitting patients are presenting, as some studies suggest, then this could predispose a cohort to globally exhibit a slower disease progression. Indeed, the cohort characteristics differ, with variation in sex as well as disease course (primary-progressive vs relapsing-onset) ratios evident (figure 1).

Relapsing–remitting and secondary-progressive MS. The majority of patients with MS (around 80%–90%) will present with a relapsing–remitting disease course, lasting around 2 decades (figure 2). Unlike time to EDSS 6, some consensus is reached surrounding this time, although there are fewer natural history studies contributing to this observation (figure 2). In the subsequent secondary-progressive phase, relapses become less prominent and relentless progression ensues, although minor remissions and plateaus can occur. Less is known about disability accrual once this phase has begun; interpretation of findings is complex as secondary-progressive MS is reached at differing levels of disability (EDSS) after different durations of the relapsing–remitting phase and in most studies, represents only a fraction of the total relapsing–remitting cohort destined to reach secondary-progressive MS.

Primary-progressive MS. Primary-progressive MS is characterized by progression from the clinical onset of MS with occasional plateaus or temporary minor improvements and typically affects around 15% of patients, although this has ranged considerably from 6% to 20% (figure 1). Time to cane (DSS/EDSS 6) also shows considerable variation, ranging from 6 to 21 years, with some suggestion of slowing in later studies (figure 1). This was echoed in a recent phase III clinical trial; a slower-than-expected disease progression was cited as partly to blame for the study’s disappointing early termination.

Late-onset MS. As the population ages, the prevalence of late-onset MS will likely increase (usually defined as 50+ years old at onset). A recent cohort study reported MS onset in an 81-year-old patient. Primary-progressive MS predominates in late-onset MS, affecting 55%–80% of individuals, although disease progression appears similar to those with adult-onset MS, once the disease phenotype is set.

Mortality and MS. Over the past 50 years, average life expectancy at birth has increased globally by almost...
Figure 1  Median time (years) to requiring a cane to walk (EDSS 6 or the equivalent) from onset of multiple sclerosis (MS)

Ninety-five percent confidence intervals (CI) shown where available. DSS = Disability Status Scale Score; EDSS = Expanded Disability Status Scale Score (EDSS 6 = “requires a cane to walk”); onset age = mean onset age for whole cohort (SD given when available); NA = not available. London, Ontario, Canada45,58; Lyon, France12,24; Olmsted County, USA13; British Columbia, Canada14,15; Nova Scotia, Canada16; Lorraine, France17. * Not explicitly published, figures derived from the authors (personal communications: S. Pittock, 2009, and M. Brown, 2009). For Nova Scotia, once treatment with an immunomodulatory drug was commenced, subsequent data for that patient were truncated. † Use of immunomodulatory drugs not reported. ‡ Updates were also conducted in 1984–1991 and 1992–1997; the focus of the figure has been the defining cohort in which the main disease progression findings were reported. Other studies of note: Göteborg, Sweden (n = 308)8,9 has been reviewed elsewhere.2 Median time to EDSS 6 was 18 years for the whole cohort. Cross-sectional studies can also provide some useful information, although with less robust estimates, the median time to and age at DSS 6 being 24 years (95% CI: 19–27, CI obtained by personal communications: P. Macaskill and J. McLeod, 2009) and 52 years (95% CI unavailable), respectively, in Newcastle, Australia (n = 159).60

Comment: Data collection methods, definition of outcomes, and the cohorts captured vary between natural history studies, influencing findings in a variety of ways. Demographic differences are also evident between studies. There are small gender differences, with the older cohorts reporting around 65% females,24,58 compared to 70–74% in later cohorts.14,16,17 Those with primary-progressive MS comprise between 6% and 20% of cohorts, with no discernable time-related pattern. The mean onset age will be influenced by the disease course (or vice versa), but overall is surprisingly similar between cohorts (approximately 30 years of age). Differences in disease progression will in part be influenced by the clinical characteristics of the cohort. However, disease progression differs between studies even when split into relevant subgroups (such as relapsing-onset and primary-progressive MS).
20 years; 13 years in Europe alone (World Health Statistics 2008). Likewise, the probability of survival has increased in MS, 21-23 although remains approximately 10 years shorter than expected from the age-matched general population, based on findings from the Danish Registry. 21 A 3-fold increased risk of death in MS during the study period compared to the general population has been reported in 3 recent cohorts from Denmark (MS onset 1949–1996, followed until 2000, n = 9,881) 21; South Glamorgan, Wales, UK (prevalent patients in 1985, followed until 2006, n = 369); and Hordaland County, Western Norway (MS onset 1953–2003, n = 878) 22 although variability exists. 23

Comment. The suggestion that MS is progressing more slowly than previously thought may represent a change in the type of patient with MS being seen in MS clinics today, perhaps driven by an increased recognition of MS, new diagnostic techniques, availability of immunomodulatory drugs to treat MS (which could influence the desire to diagnose), and increased survival (related to better health care and management of chronic diseases). All these factors might contribute to the differences between older and newer natural history studies.

Factors associated with MS disease progression. Using age at disability milestones to challenge well-held beliefs. Clinical characteristics associated with disability progression (to both EDSS 6 and secondary progression) are shown in figure 1. Men and those older at MS onset are often reported as having a poorer outcome. Indeed, both groups progressed more rapidly to EDSS milestones from onset in the majority of studies (table 2). 2,14,17,24,25 However, those older at onset were consistently older when reaching EDSS 6 than those younger at onset. 11,14 This has also been demonstrated in pediatric MS. 36 Consequently, those older at onset could be viewed as having a better outcome—not only do they remain disease-free for a longer period of time, they will also, on average, be older when reaching fixed disability milestones compared to those younger at onset.
<table>
<thead>
<tr>
<th>Location</th>
<th>Clinic vs population-based</th>
<th>Setting</th>
<th>Diagnostic criteria</th>
<th>Prospective vs retrospective</th>
<th>Mean follow-up/y (SD)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>London, Ontario, Canada</td>
<td>Population and clinic-based (subpopulation of Middlesex County, ~90% captured)</td>
<td>One outpatient MS specialist clinic</td>
<td>Probable or possible MS, Poser criteria</td>
<td>Retrospective and prospective</td>
<td>a) From onset: 11.9 years (^{6,58}); b) from first clinic visit: NA (^{9.8\text{ (SD 7.9)}}) for PPMS only, (n = 218\text{ (22)}}); 1972-1994 cohort</td>
<td></td>
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<tr>
<td>Lyon, France</td>
<td>Clinic-based, but &quot;representative of the general population&quot; (^{24})</td>
<td>One outpatient clinic, serving as the referral center for the city of Lyons and the Rhône-Alpes region since 1976 (^{2})</td>
<td>Definite or probable MS (Poser) (^{24})</td>
<td>Retrospective from onset to first clinic visit; prospective thereafter (^{1,2})</td>
<td>a) From onset: 11 (SD: 10) (^{24}); b) from first clinic visit: NA (\text{mean time to first clinic visit} = 6\ (SD 8))\</td>
<td>Each natural history study has its own strengths and weaknesses. Many studies claim to be population-based, but in reality, this can be difficult to prove. In those that do have a population-based cohort (often nested in the larger study), these are usually based on 1 small geographical area, with patients referred to 1 specialist clinic—how representative these small cohorts are of wider populations is unknown. Data collection and definition of outcome differs between studies and in a disease which progresses over decades, these will probably have the greatest impact. Prospective data collection potentially brings increased accuracy, unless patient assessments are very infrequent and the outcome of interest is reached in between these sparse examinations; retrospective assignment results in fewer excluded patients, but less certainty.</td>
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<tr>
<td>Olmsted County, MN, United States</td>
<td>Population-based (^{13})</td>
<td>Patients seen at the Mayo Clinic, the Olmsted Medical Group, or the Olmsted Community Hospital (^{13})</td>
<td>Definite MS, Poser criteria (^{13})</td>
<td>Retrospective</td>
<td>a) From onset: 19.3 (median) (^{13}); b) from first clinic visit: NA</td>
<td></td>
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<tr>
<td>British Columbia, Canada</td>
<td>Population-based; ~80% captured (^{14})</td>
<td>All 4 outpatient MS specialist clinics in the province of British Columbia (^{14})</td>
<td>Definite MS, Poser criteria (^{14})</td>
<td>Retrospective from onset to first clinic visit; prospective thereafter (^{1,4})</td>
<td>a) From onset: 20.1 (SD 9.9) (^{14}); b) from first clinic visit: 8.0 (6.2) (^{14})</td>
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<tr>
<td>Nova Scotia, Dalhousie</td>
<td>Clinic-based, but &quot;representative of the general population&quot; (^{16})</td>
<td>Nova Scotia's only specialized referral service for MS (^{16})</td>
<td>Definite MS, Poser or McDonald criteria (^{16})</td>
<td>Retrospective from onset to first clinic visit; prospective thereafter (^{1,6})</td>
<td>a) From onset: NA; b) from first clinic visit: NA</td>
<td></td>
</tr>
<tr>
<td>Lorraine, France</td>
<td>Population-based (^{20})</td>
<td>The Lorraine MS Regional Network, comprising neurologists (of fice-based practice and hospitals), MS centers, radiologists, biologists, nurses, physiotherapists, and the Multiple Sclerosis Association (^{20})</td>
<td>Definite or probable MS (Poser) (^{17})</td>
<td>Retrospective and prospective (^{20})</td>
<td>a) From onset: 13.7 (SD 9.7) (^{17}); b) from first clinic visit: NA</td>
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**Table 1** Characteristics of the main longitudinal natural history studies published over the last decade

*Abbreviations: MS = multiple sclerosis; NA = not available; PPMS = primary-progressive multiple sclerosis.*

*Studies have been placed in approximately chronological order, starting with the oldest. Where cohorts/studies have had updates, the focus of the table has been the defining cohort in which the main disease progression findings were reported (which are included in figures 1 and 2). Another older longitudinal population-based natural history database worthy of mention includes Göteborg, Sweden \(n = 308\) \(^{8,9}\) which has been reviewed elsewhere. \(^2\)
<table>
<thead>
<tr>
<th>Location</th>
<th>Endpoint</th>
<th>From onset of MS</th>
<th>From birth (i.e., age of the patient at disability milestones)</th>
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<tr>
<td></td>
<td></td>
<td>Positively associated (better outcome)</td>
<td>Not associated</td>
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<tr>
<td></td>
<td></td>
<td>Positively associated (better outcome)</td>
<td>Not associated</td>
</tr>
<tr>
<td>Göteborg, Sweden</td>
<td>DSS 6</td>
<td>Younger onset age&lt;sup&gt;5&lt;/sup&gt;; monoregional onset symptoms&lt;sup&gt;6&lt;/sup&gt;; RR disease course&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Gender&lt;sup&gt;9&lt;/sup&gt;; specific onset symptoms: optic neuritis, brainstem, spinal symptoms&lt;sup&gt;6&lt;/sup&gt;; season of birth&lt;sup&gt;14&lt;/sup&gt;</td>
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<tr>
<td>London, Ontario, Canada</td>
<td>DSS 6</td>
<td>Female gender&lt;sup&gt;25&lt;/sup&gt;; younger onset age&lt;sup&gt;25&lt;/sup&gt;; RR disease course&lt;sup&gt;25&lt;/sup&gt;; onset symptoms: presence of optic nerve involvement; absence of motor (insidious) or limb ataxia/balance symptoms&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Onset symptoms: sensory, motor (acute), diplopia, and/or vertigo&lt;sup&gt;25&lt;/sup&gt;</td>
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<tr>
<td>Lyon, France</td>
<td>EDMUS impairment scale (DSS adapted)</td>
<td>Female gender&lt;sup&gt;24&lt;/sup&gt;; younger onset age&lt;sup&gt;24&lt;/sup&gt;; onset symptoms: presence of optic neuritis; absence of long-tract involvement&lt;sup&gt;24&lt;/sup&gt;; RR disease course&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Brainstem involvement&lt;sup&gt;24&lt;/sup&gt;</td>
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<tr>
<td>Lyon, France</td>
<td>SPMS</td>
<td>Female gender&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Onset symptoms: long tracts, optic neuritis, brainstem&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>British Columbia, Canada</td>
<td>EDSS 6</td>
<td>Female gender&lt;sup&gt;14&lt;/sup&gt;; younger onset age&lt;sup&gt;14&lt;/sup&gt;; RR disease course&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Onset symptoms: motor, sensory, optic neuropathy, or cerebellar, ataxia, or brainstem&lt;sup&gt;14&lt;/sup&gt;; month or season of birth&lt;sup&gt;14&lt;/sup&gt;</td>
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<tr>
<td>British Columbia, Canada</td>
<td>SPMS</td>
<td>Female gender&lt;sup&gt;4&lt;/sup&gt;; younger onset age&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Onset symptoms: motor, sensory, optic neuropathy, or cerebellar, ataxia, or brainstem&lt;sup&gt;4&lt;/sup&gt;; month or season of birth&lt;sup&gt;14&lt;/sup&gt;</td>
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<tr>
<td>Groningen, the Netherlands</td>
<td>EDSS 6</td>
<td>Younger onset age&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Gender&lt;sup&gt;2&lt;/sup&gt;; onset symptoms: motor, sensory, optic neuritis, brainstem/cerebellar; other (such as sphincter dysfunction or sexual symptoms); month or season of birth&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>Groningen, the Netherlands</td>
<td>SPMS</td>
<td>--</td>
<td>Month or season of birth&lt;sup&gt;28&lt;/sup&gt;</td>
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<tr>
<td>Lorraine, France</td>
<td>EDSS 6</td>
<td>Female gender&lt;sup&gt;17&lt;/sup&gt;; younger onset age&lt;sup&gt;17&lt;/sup&gt;; RR disease course&lt;sup&gt;17&lt;/sup&gt;; onset symptoms: monosymptomatic&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Onset symptoms: isolated optic neuritis, isolated dysfunction of long tracts, or isolated brainstem dysfunction&lt;sup&gt;17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lorraine, France</td>
<td>SPMS</td>
<td>Female gender&lt;sup&gt;17&lt;/sup&gt;; younger onset age&lt;sup&gt;17&lt;/sup&gt;; onset symptoms: monosymptomatic&lt;sup&gt;13&lt;/sup&gt;</td>
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Abbreviations: DSS = Disability Status Scale score; EDSS = Expanded Disability Status Scale score (EDSS 6 = requires a cane to walk); EDMUS = European Database for Multiple Sclerosis; MS = multiple sclerosis; NA = not available; RR = relapsing-remitting; SPMS = secondary-progressive MS.

* Studies have been placed in approximately chronological order, starting with the oldest. Findings from multivariate analysis reported where possible.
pared to their younger-at-onset counterparts. Similarly, a recent study found the median age at which EDSS 6 was reached differed little for men and women, being around 60 years of age for both ($p = 0.082$). However, these findings need to be corroborated as others found a 4-year age gap between men and women when reaching DSS 6. A relapsing-remitting disease course from onset is consistently associated with a favorable outcome; these patients were also older when reaching (most) disability milestones compared to those with primary-progressive MS.

**Factors associated with the progressive phases.** Men and those older at onset appear to exhibit a shorter time to secondary-progressive MS (figure 2 and table 2).\(^{4,5,7,17,27}\) the potential consequence being a narrower window of therapeutic opportunity at which the (current) immunomodulatory drugs likely have maximal benefit.\(^{4}\) From onset of secondary-progressive MS, men still appear to progress more rapidly than women in some\(^{4}\) but not all studies.\(^{5,9}\) although both men and women with secondary-progressive MS seem to reach EDSS 8 (become wheelchair-bound) at around the same age.\(^{4}\)

In primary-progressive MS, few clinical predictors of disease progression have been found, other than sooner to cane, sooner to wheelchair.\(^{10,15,28}\) Biomarkers might provide further insight: a reduction in brain volume over 2 years was associated with a worse (EDSS) outcome 8 years later in a multicenter study of 101 primary-progressive patients;\(^{39}\) gray matter magnetization transfer ratio showed promise from a shorter 3-year study of 47 primary-progressive patients.\(^{30}\)

Age has long been associated with the progressive phases; a shared age at the onset of primary-progressive and secondary-progressive MS has been found by some,\(^{31-34}\) but not all,\(^{35}\) fueling debate over whether the 2 progressive phases are distinct entities or share a similar pathway with perhaps a common mechanism of structural degeneration in the CNS. However, comparisons could be compromised by disregarding patients who had not yet reached secondary-progressive MS at the end of follow-up, especially when patients were not followed long enough. Based on this problem, the age at progression cannot be taken as evidence that primary-progressive and secondary-progressive MS are comparable.\(^{35}\) Further pathologic, paraclinical, and laboratory studies are needed to address whether the underlying pathology and axonal destruction in the progressive phases is driven by the same underlying mechanisms. Nonetheless, age appears an important player in neurodegenerative disease.\(^{36}\)

Pathophysiologically, an older age is associated with reduced synaptic plasticity, less efficient remyelination, and impaired oligodendrocyte progenitors.\(^{36}\)

**Other associations.** Month of birth might influence risk of disease in those with relapse-onset MS,\(^{37}\) but neither month nor season of birth appear to alter subsequent disease progression (table 2).\(^{8,38}\) Onset symptoms do not appear reliable independent predictors of disease progression (table 2). The absence of CSF oligoclonal immunoglobulins (approximately 3% of patients with MS) appears associated with a longer time to DSS 6 compared to those with oligoclonal banding (hazard ratio 0.51; 95% confidence interval 0.27–0.94; $p = 0.03$).\(^{39}\) Further, patients negative for both HLA-DRB1*15 and oligoclonal banding were 10 years younger when reaching EDSS 6 compared to those positive for both.\(^{40}\) Most imaging, biologic, or surrogate markers tend to be collected as part of cross-sectional or short-term cohort studies, comprehensive reviews of which can be found elsewhere. Special mention is given to a small but valuable cohort of patients with clinically isolated syndrome (i.e., a single neurologic attack compatible with MS); 107/140 (75%) were followed for a mean of 20 years; 67/107 (63%) fulfilled diagnostic criteria for MS, and T2 lesion volume changes and gray matter atrophy (but not white matter atrophy), particularly in the first 5 years, were associated with increased disability at 20 years and development of secondary-progressive MS.\(^{41}\)

**Relapses and disease progression: An apparent dissociation.** Relapses naturally decrease in frequency over time in most but not all studies.\(^{42}\) Whether relapses have a long-term impact on disease progression has been a matter of debate. Evidence from shorter-term studies\(^{43}\) or reevaluation of clinical trial data\(^{44}\) is difficult to interpret given the resolution of short-term deficits with longer-term follow-up. Longer-term studies typically focus on relapses that occur in the very early years after symptom onset (within 2 to 5 years postonset).\(^{8,9,17,24,25,45,46}\) although application of a newer statistical technique (time-dependent survival analyses) allowed one group to examine the impact and timing of relapses beyond this early window.\(^{47}\)

There appears to be general agreement that complete or near complete recovery from the first attack is indicative of a slower progression to disability milestones\(^{8,17,24,25}\) or secondary progression\(^{17}\) (table 3). It is uncertain whether time between the first 2 attacks affects long-term prognosis as immortal time bias could impact findings. Fewer relapses in the first 2 to 5 years were associated with a longer time to disability milestones and secondary-progressive MS in most\(^{8,17,24,25,47}\) but not all studies.\(^{8}\) However, the
The long-term impact of these relapses was minimal.47 Furthermore, later relapses (occurring \(5–10\) or \(10\) years postonset) had a diminishing impact on disease progression, with minimal effect on long-term disease progression (either to EDSS 6 or secondary progression).47 Age may modify findings; relapses had a greater impact on disability progression in younger patients (\(<25\) years at MS onset) than older patients (\(\geq35\) years).47

General dissociation between relapses and disability has been shown by comparing disease progression between specific groups of patients.10,12,24,31–32,35 Specifically, once a certain disability level12 or the progressive phase was reached, progression thereafter (to higher fixed disability milestones) appeared similar in most studies for most subgroups examined,12,24,32,35 but not all.10,12,31,35 In particular, disease progression to DSS 6, 8, or 10 was similar (once the progressive phase was reached) between primary-progressive MS and particular forms of progressive MS (including early converters to secondary-progressive MS [by DSS 2 or 3] or patients termed single attack progression, where only a single attack occurs before the onset of progression).32 Relapses also appear to have little long-term effect once secondary progression has begun.12,47 Findings have several practical implications. First, results impact knowledge surrounding prognosis, providing some reassurances for patients presenting with a previous history of relapses, that as time elapses, earlier events will have a diminishing impact on the current situation. In addition, relapses occurring later in life likely have a lesser long-term impact than former events.47 Secondly, findings are suggestive that immunomodulatory drugs (which mechanistically target the inflammatory processes in MS) may not substantially impact long-term disease progression.12,47 However, windows of opportunity might exist in younger patients early in the disease course.47 Finally, findings support the growing need for drugs targeting axonal destruction, the presumed driver of irreversible disability.

Comment. MS is a heterogeneous disease, with many disease trajectories. Better predictors of disease progression are needed; further work is required to identify and perhaps combine risk factors which in the future might include a mix of demographics, clinical characteristics, imaging, pathology, lesion site, lesion type, a blood or CSF biomarker, genom-

<table>
<thead>
<tr>
<th>Location</th>
<th>Endpoint</th>
<th>From onset of MS</th>
<th>Not associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Göteborg, Sweden</td>
<td>DSS 6</td>
<td>Complete or near complete recovery from first attack(^4)</td>
<td>Total number of relapses in the first 2 or 5 years; time between the first 2 attacks (time to endpoint measured from the second attack)(^6)</td>
</tr>
<tr>
<td>Lorraine, France</td>
<td>EDSS 6</td>
<td>Complete recovery from first attack(^1); longer time between the first 2 attacks; fewer relapses in the first 5 years(^6)</td>
<td>—</td>
</tr>
<tr>
<td>Lorraine, France</td>
<td>SPMS</td>
<td>Complete recovery from first attack(^1); longer time between the first 2 attacks; fewer relapses in the first 5 years(^6)</td>
<td>—</td>
</tr>
<tr>
<td>Lyon, France</td>
<td>EDMUS impairment scale (DSS adapted)</td>
<td>Complete recovery from first attack(^2); longer time between the first 2 attacks; fewer relapses in the first 5 years(^6)</td>
<td>—</td>
</tr>
<tr>
<td>Lyon, France</td>
<td>SPMS</td>
<td>Longer time between the first 2 attacks(^3)</td>
<td>—</td>
</tr>
<tr>
<td>London, Ontario, Canada</td>
<td>DSS 6</td>
<td>Longer time between the first 2 attacks(^5); fewer relapses in the first 2 years(^6)</td>
<td>—</td>
</tr>
<tr>
<td>British Columbia, Canada</td>
<td>EDSS 6</td>
<td>Lower relapse rate in the first 5 years(^6)</td>
<td>Long-term impact of a relapse occurring within 5 years, &gt;5–10 years, or 10 years postonset was minimal(^4)</td>
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</table>

Abbreviations: DSS = Disability Status Scale score; EDSS = Expanded Disability Status Scale score (E/DSS 6 = requires a cane to walk); EDMUS = European Database for Multiple Sclerosis; MS = multiple sclerosis; SPMS = secondary-progressive MS.

* Studies have been placed in approximately chronological order, starting with the oldest. Findings from multivariate analyses reported where possible.

b Findings are subject to bias as the time to endpoint was measured from onset of MS rather than from the second attack, which introduces immortal time bias, recently highlighted as a major source of bias.

Table 3 The impact of relapses (attacks) on time to DSS/EDSS disability milestones and secondary-progressive MS*
ics, and proteomics. These studies might also help clarify whether MS reflects 1 disease or different diseases with different etiologies but some clinical and pathologic commonalities. Generally, the long-term impact of relapses appears more evident early during the disease. Windows of risk or windows of opportunity might exist for certain groups of patients, in particular those younger at MS onset.

**Natural history of special cohorts. Benign MS.** Benign MS understandably represents a desired disease trajectory. Over 10 different definitions of benign MS exist, the most common being EDSS ≤3 after 10 years disease duration.\(^{48,49}\) Using this definition, from a recent population-based study, 30% of patients were deemed benign.\(^{50}\) In a group of patients with clinically isolated syndrome, of those who later developed definite MS over the subsequent 20 years, 39% (26/67) were considered benign (EDSS ≤3).\(^{41}\)

The quiescent nature associated with benign MS makes this one of the most difficult groups to follow longitudinally; patients can be reticent to come to a clinic full of wheelchairs, and systematic loss of these patients can bias findings. Nonetheless, benign MS appears to be transitory for many, with only 52% (88/169) of clinic-based patients with MS who were benign at 10 years (EDSS ≤3) remaining so at 20 years.\(^{40}\) Modifying the definition of benign MS (to an EDSS ≤2)\(^{10}\) results in only a slightly higher proportion of patients remaining benign, with around 68%\(^{40,50}\) doing so at 20 years (findings were strikingly similar in both the Mayo and BC clinic cohorts). Benign MS outpatients at St. Vincent’s Hospital, Dublin, were followed up 21 years later, by which time 15% remained benign whether defined with EDSS cutoffs of ≤3 or EDSS ≤2.\(^{48}\) All these studies had an 85% or greater follow-up.\(^{48-50}\)

Good predictors of benign MS remain elusive, although 1 study did find that women, those younger at onset, and those without motor onset symptoms were more likely to be considered benign at some point in their disease.\(^{40}\) Predictors of remaining benign are also few, other than the presence of a low EDSS score.\(^{49,51}\) However, other MS disease aspects, such as cognition, are not well-captured by the EDSS and may present a significant burden, even in benign MS, with some studies associating this with a poorer outcome.\(^{52-54}\)

**Malignant MS.** The converse of benign is malignant MS, although relatively little appears known about its occurrence or related epidemiology. Interestingly, HLA-DRB1*01 or a tightly linked region appears underrepresented in malignant MS (EDSS >6 within 5 years; \(n = 51\)).\(^{55}\)

**Familial MS.** Cross-sectional studies have shown that disease severity appears unrelated to whether one has family members with MS or not (\(n = 1,083;\) Genetic Analysis of MS in Europeans Study),\(^{56}\) echoing earlier studies. However, genetic loading was associated with a shorter time to secondary progression\(^{56}\) and younger age at primary-progressive MS in 1 small study (\(n = 313;\) Groningen, the Netherlands)\(^{57}\) as well as an increased risk of presenting with primary-progressive MS.\(^{56}\)

**Comment.** Little appears known about malignant MS. More systematic studies on the extremes of MS may help us to identify further disease-modifying factors such as functional polymorphisms in relevant genes. Larger longitudinal studies are also needed to confirm or refute whether genetic loading alters disease progression.

**DATA COLLECTION AND METHODOLOGIC ISSUES IN MS NATURAL HISTORY STUDIES**

The ideal MS natural history study would perhaps prospectively monitor all patients in a geographic location from onset until death, with regular follow-up, capturing detailed exposure and outcome data, from physical disability to cognition, employment, and quality of life. Clearly this is not possible—measurements of MS outcome are not always ideal, and some patients, often primary progressive or even benign, take many years before symptoms are recognized as being related to MS.

**Impact of censoring on findings.** When examining the time to a disability milestone, survival analysis (Kaplan-Meier, Cox regression, or in earlier studies, life tables) is appropriate, being able to take into account patients not reaching the milestone at last follow-up (right-censoring). This is particularly important in MS as censoring rates can be high, ranging from 51% to 72% for time to EDSS/DSS 6.\(^{12,14,17,58}\) While there has been some debate as to whether the censoring rate itself is a source of bias in MS,\(^{2}\) the statistical literature has already established that the causes of censoring rather than the actual rates are more important when considering bias.\(^{59}\) Other types of censoring exist—left-censoring, whereby a patient has already reached the milestone when first assessed, or interval-censoring, where a patient is known to have reached the milestone between clinical visits. Dealing with these issues varies, is not always explicitly reported, and likely contributes to variation between studies; for instance, trying to retrospectively determine specific (typically low) EDSS scores (missing because a patient has already passed these levels of disability, i.e., is left-censored) is likely unreliable and will not be the same as prospectively collected data. This can be particularly problematic in certain subgroups, such as primary-progressive MS, where the average DSS/EDSS scores at first
clinics visit can be high (being 5 in both British Columbia and London, Ontario\textsuperscript{16,15}), making time to moderate disability (i.e., lower disability outcomes) unreliable.

Comment. Issues related to censoring in MS natural history studies are important and currently an underexplored source of variation between studies. More efforts should be channeled into examining reasons for censoring: delays in coming to clinic, sporadic attendance at clinic, and lost to follow-up will all contribute.

LOOKING BACK AND MOVING FORWARD Several important advances have been made in our understanding of MS natural history; findings impact the prognosis given to patients, affect clinical trial design, and shape clinically the way we think about MS. Despite advances, many questions remain unanswered. Although methodologic differences exist between studies, why findings are so disparate needs to be fully resolved; changes in disease progression over time could have occurred, but methodologic differences cannot be ruled out. Consensus surrounding methodologic approaches is needed. MS is also a multifaceted disease, such that use of diverse outcome measures in population-based cohorts would be valuable to provide a more encompassing picture. Advances in the analysis of MS disease progression are underway, including Markov transition models or nonlinear regression models, although these rely on more complex assumptions. Good predictors of disease progression remain elusive, particularly in the individual. Developments such as an online analytical processing tool by the Sylvia Lawry Centre for Multiple Sclerosis Research might prove useful in paving the way toward a practical prognosis for the individual with MS. The application of -omics (genomics or proteomics) to personalize prediction of the MS disease trajectory is a tantalizing concept, yet to be realized. Interactions with environmental/modifiable factors which might influence the MS disease course (such as smoking, infections, obesity, comorbidities, exercise, sunlight exposure, diet, or vitamin D status) have not been covered here, but incorporation into large longitudinal studies would be worthwhile. Natural history studies also have additional, relatively untapped applications, such as the possible identification of commonly used drugs (e.g., antidepressants or statins) which might influence the MS disease course. Finally, although the widespread use of immunomodulatory drugs for MS potentially heralds our last opportunity to examine the real natural history of MS, this should not deter close monitoring of patients in clinical practice as many questions remain not yet fully answered, including the impact of immunomodulatory drugs on long-term disability progression.

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