The natural history of secondary progressive multiple sclerosis

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ABSTRACT

Background The onset of secondary progression is a pivotal event in the course of relapsing–remitting (RR) multiple sclerosis (MS). Patients with secondary progressive MS (SPMS) experience continuous worsening of symptoms independent of the occurrence of relapses. Possible risk factors associated with the onset of SPMS remain under investigated in natural history studies of MS disease course.

Methods We used Kaplan–Meier survival analyses and Cox regression models to investigate the influence of gender, onset age and onset symptoms on time to and age at SPMS in British Columbia (BC) MS patients with a RR disease onset who were not exposed to immunomodulatory drugs.

Results Of 5778 patients in the BCMS database with definite MS, 5207 (90%) had an RR onset. Median time to SPMS was 21.4 years (95% CI 20.6 to 22.2), reached at a median age of 53.7 years (95% CI 53.1 to 54.3). Male gender and motor onset symptoms were associated with a shorter time to and younger age at SPMS. A younger age at disease onset was associated with a longer time to SPMS but also with a younger age at secondary progression. Other onset symptoms were not associated with time to, or age at, SPMS.

Conclusions We identified three factors influencing the onset of SPMS in untreated patients with RRMS: motor onset symptoms and male gender were associated with both a shorter time to and a younger age at SPMS. A younger age at disease onset should not be viewed as indicating a better prognosis.

INTRODUCTION

Natural history studies of multiple sclerosis (MS) often focus on the time from disease onset until patients reach certain landmark disability scores (such as Expanded Disability Status Scale (EDSS) 6.0, when a cane is required for walking, or EDSS 8.0, when a patient is mostly restricted to a wheelchair). Besides the accumulation of disability, patients with relapsing–remitting MS are also at risk of experiencing a critical change in their disease course—the development of secondary progression.1

A secondary progressive disease course has developed when a patient’s clinical condition starts to deteriorate steadily and independently of relapses. Patients with secondary progressive MS (SPMS) have an unfavourable prognosis and can expect a slow and unremitting worsening of their ability to function.2 The onset of secondary progression is therefore another important outcome to examine in natural history studies.

The onset of secondary progression has been addressed by several small studies that may have had limited power and have often focused on patients who had already reached SPMS.3–5 Tremlett et al have previously investigated a subset of the British Columbia MS (BCMS) cohort6 but when examining predictors of progression were unable to fully adjust findings for the different patient characteristics considered. Here we expand findings by examining the entire available cohort and by fitting a multivariable model when considering possible predictors of progression. For the present study, we investigated the natural history of secondary progression in immunomodulatory drug (IMD) naïve patients by examining factors associated with the time from onset to the development of SPMS in the whole BCMS cohort of relapsing at onset patients. Because MS is a chronic, lifelong disease, the age at which patients reach the progressive phase is important and relevant to patients and their physicians; we have therefore also examined the factors that influence the age at which SPMS develops.

METHODS

Clinical information

The clinical information was taken from the British Columbia MS (BCMS) database, a longitudinal database linking the four MS clinics in British Columbia, Canada, and capturing prospective data for over 80% of the MS population in the province.7 8 We selected all patients with a diagnosis of clinically definite MS according to the Poser diagnostic criteria,9 with a relapsing at onset disease course who were enrolled in the database from 1 September 1980 to 31 July 2003. SPMS disease course was defined clinically by the treating neurologist as a progressive course following a relapsing–remitting onset.10 Follow-up visits typically occurred annually. In order to investigate the natural history of the disease without the possible influence of IMDs, patients who received such treatments were censored at the first day of treatment. Gender, age at disease onset and onset symptoms (motor, sensory, optic neuritis and cerebellar/ataxia/brainstem), recorded at the patient’s first BCMS clinic visit, were also extracted from this database. Age at onset was divided into four categories: <30 years, 30 to <40, 40 to <50 and ≥50 years. The main outcome measures were the time from disease onset and from birth to the onset of secondary progression.

Statistics

The time from disease onset to onset of secondary progression and the age at secondary progression (ie, time from birth to SPMS) were estimated from...
Kaplan–Meier survival analyses. Group differences in survival time were compared with log rank tests. In addition, we built multivariable Cox regression models with time to secondary progression and age at secondary progression as the dependent variables. Covariates included in these models were gender, onset symptoms and age at disease onset for the time from onset to secondary progression, and gender and onset symptoms for the age at secondary progression. The age at disease onset was not included as a covariate in the model for age at secondary progression because its value is necessarily smaller than the outcome in every case. The latter model was stratified by age at disease onset instead. We tested for possible violations of the proportional hazards assumption in these multivariable models with log minus log plots and Schoenfeld residuals.

All statistical analyses were performed with the SPSS statistical software package V.16 (SPSS Inc).

RESULTS
Patient cohort
Of 5778 patients with definite MS, 5207 (90%) had a relapsing–remitting onset. IMDs had been used by 1249 (24%) patients; these patients were censored at the first day of treatment. The date of onset of secondary progression was unavailable for 38 patients (0.7%); these patients were censored at the last day of follow-up. The date of onset of secondary progression was unavai-

able for 38 patients (0.1%); these patients were censored at the end of follow-up. The time of disease onset was unknown for all analyses. The time of disease onset was unknown for a further seven patients (0.1%); these patients were excluded from the analyses of the time to secondary progression from onset of MS and from the stratified Cox regression analysis of predictors of age at SPMS. Of the 5169 available patients, 1821 (35%) had reached SPMS by the study end.

Kaplan–Meier survival analyses
The results of the Kaplan–Meier survival analyses are shown in table 1. Median time to secondary progression was 21.4 years from onset (95% CI 20.6 to 22.2 years) and median age at secondary progression was 53.7 years (95% CI 53.1 to 54.3 years). There was wide variability in survival estimates in both the time to and the age at secondary progression: while the 25% of patients with the quickest disease progression reached secondary progression in less than 11.4 years and at a younger age than 45.1 years (first quartile estimated from the Kaplan–Meier analysis), the 25% with the slowest progression reached secondary progression after more than 32 years and at an age of more than 65.1 years (last quartile). Men and patients with motor onset symptoms developed SPMS after a shorter time and at a younger age (see table 1 and figures 1 and 2). Patients with a younger age at onset took a longer time to SPMS but reached SPMS at a younger age (p<0.0005) (figure 5).

Multivariable regression models
The results of the multivariable Cox regression models are shown in table 1. Male gender and the presence of motor onset symptoms were independently associated with a shorter time to, and a younger age at, SPMS (table 1). Younger age at disease onset was associated with a longer time to SPMS; the hazard

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Kaplan-Meier estimates and multivariable HRs of time to and age at secondary progression by potential risk factors</th>
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<tr>
<td>Factor</td>
<td>Overall</td>
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<tr>
<td>Overall</td>
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</tr>
<tr>
<td>Gender</td>
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<tr>
<td>Men</td>
<td>1370</td>
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<tr>
<td>Age at onset (years)*</td>
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<tr>
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<td>2533</td>
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<tr>
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<td>40 to &lt;50</td>
<td>761</td>
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<tr>
<td>50 and above</td>
<td>188</td>
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<tr>
<td>Onset symptoms</td>
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<tr>
<td>Motor</td>
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<tr>
<td>Present</td>
<td>1031</td>
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<tr>
<td>Sensory</td>
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<tr>
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<tr>
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<tr>
<td>ON</td>
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<tr>
<td>Absent</td>
<td>4251</td>
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<tr>
<td>Present</td>
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*Seven patients for whom date at disease onset was unknown were excluded from all analyses of time to SPMS and from the analysis of the association between age at onset and age at SPMS.
†Derived from Cox regression analyses.
‡HRs represent a per year increase in risk.
rate (HR) of reaching SPMS increased by 27.1% (95% CI 23.4 to
30.9%) for every 5 year increase in onset age (HR per 1 year
increase: 1.05 (95% CI 1.04 to 1.06)).

Other onset symptoms were not associated with these
outcomes. Our investigation of all models with log minus log
plots and Schoenfeld residuals showed no evidence of a violation
of the proportional hazards assumption

**DISCUSSION**

We have reported on the long term follow-up of a cohort of
relapsing at onset MS patients from a population based MS
database in British Columbia, Canada. We found the onset of
secondary progression to be a gradual process in the cohort as
a whole, with a steady increase of conversions to SPMS observed
over follow-up. However, the window was wide, with SPMS
being reached within 1 year of MS onset through to more than
50 years post-onset, and in individuals from 11 to 82 years of age.

Overall, the median time to SPMS was 21.4 years, which is
similar to that reported for the few other cohorts in which
survival analyses have been applied, including 19.1 years in
Lyon
11 and 20.0 years in Lorraine, France.

Three factors were associated with the onset of secondary
progression in our cohort: gender, age at onset and motor onset
symptoms.

Male gender predicted a shorter time to, and a younger age at,
SPMS in our cohort. The influence of male gender on the time to
onset of SPMS has been controversial—while some previous
studies suggested that men have a worse prognosis than
women,
6 11 13 other studies have found no such association.
14–18 Sex hormones may play a role in this gender difference—an
increase in oestrogen levels in particular is believed to reduce
CNS inflammation.
19 Relapse frequency is also reduced during
pregnancy and shows a rebound after delivery. This phenom-
enon has been associated with the rise and fall of oestrogen and
progesterone levels during pregnancy and the postpartum
period.
20 Furthermore, the administration of oral oestradiol in
women with MS resulted in a decrease in the number and
volume of gadolinium enhancing lesions on cranial MRI in one

![Figure 1](image1.png)

**Figure 1** Kaplan–Meier curves showing time to (A) and age at (B) secondary progression by gender.

![Figure 2](image2.png)

**Figure 2** Kaplan–Meier curves showing time to (A) and age at (B) secondary progression by motor onset symptoms.
The main strength of this study is the fact that we have investigated a large population based cohort followed for a long time period with prospectively collected data. A limitation of our study, however, is the fact that an estimated 20% of the MS patients in BC have not been captured by the database; we are unable to determine if these other MS patients in BC would have progressed to SPMS faster or slower than the patients included in this study. On the other hand, there is no reason to believe that factors such as gender, onset symptoms and age at onset would have any different effect on disease course among those not included in the database.

Recent research suggests that the use of IMDs may influence the timing of secondary progression. It in this study, we concentrated on untreated patients to evaluate which factors are relevant in the natural history of the disease and to provide a treatment naive comparison for future cohort studies. This information may also be helpful for the design of randomised controlled trials of the effect of IMDs on conversion to SPMS.

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Competing interests PR serves on scientific advisory boards for Merck Serono, Novartis, Teva Pharmaceutical Industries Ltd and Bayer-Schering Pharma. He also serves on the editorial advisory board of Therapeutics in Neurology and has received speaker and/or consulting honoraria from Bayer-Schering Pharma, Biogen Idec, Merck Serono, Novartis and Teva Pharmaceutical Industries Ltd. HT has received speaker honoraria from the Swiss MS Society and the University of British Columbia MS Research Program.

Ethics approval The study was approved by the clinical research ethics board of the University of British Columbia.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
Information for patients from JNNP

Three traits may help predict MS prognosis

A trio of factors may help forecast how quickly early-stage multiple sclerosis progresses to a more advanced stage, reports a new study. Researchers found that two factors – being male and having movement problems early on - increase the chances that a person's disease will get worse faster. On the other hand, being diagnosed at a younger age may indicate a slower progression, although not a better prognosis overall.

What do we know already?

If you have multiple sclerosis (MS), the nerves in your brain and spinal cord slowly lose their coating. Over time, these nerves get damaged and may stop working properly, which can lead to difficulty moving your arms and legs, loss of vision, and other problems around your body. However, many people diagnosed with early MS – called relapsing-remitting MS – live a long time without serious problems. If you have this type, you get bouts of symptoms (relapses), after which your symptoms may clear up completely (remit). You may stay in remission for months or even years. However, eventually many people develop a more serious form of the disease in which some symptoms remain after a relapse and get worse over time (called secondary progressive MS). But how soon this occurs varies widely, with some people still having the mild form of MS after 30 or more years. Studies have looked for clues about which people with MS might be most likely to progress more quickly, but overall these trials have been small and not very reliable.

Researchers have now done a large, long-term study looking at 5,169 people diagnosed with relapsing-remitting MS in Canada. Using health records, they tracked who developed secondary progressive MS – and how quickly – over 20-plus years, from September 1980 through July 2003. In particular, they were interested in whether people’s sex, age at diagnosis, and early symptoms might be linked to how quickly their disease progressed.
What does the new study say?

Over the course of the study, 1,821 people (35 percent) developed secondary progressive MS (SPMS). People progressed to this later stage at very different rates. Those with the fastest progression developed SPMS less than 12 years after their initial MS diagnosis, while those with the slowest progression took more than 32 years.

Men were more likely than women to progress quickly. This wasn't entirely surprising, as other studies have suggested that the female hormone oestrogen may help protect against nerve damage. The researchers also found a higher chance of early progression among people who had movement problems (motor symptoms) when they were first diagnosed with MS. However, they didn't find any link with other types of early symptoms, such as vision problems or numbness.

People diagnosed with MS at a younger age generally had a slower progression, which confirms previous findings. But the researchers point out that this doesn't necessarily translate into a better long-term outlook. Although people diagnosed at a younger age may take longer to convert to SPMS, they are still typically younger at the onset of this more advanced stage.

How reliable are the findings?

This was a large and well-conducted study. The researchers gathered their information from a robust database of health records, covering more than 80 per cent of people with MS in British Columbia, Canada. In their analysis, they looked only at people who weren't taking medicines that can slow the progression of MS, called immunomodulatory drugs (IMDs). This makes it more likely that their results reflect genuine trends in the natural course of MS. However, this type of study can't tell us why certain factors may be associated with a faster onset of secondary progressive MS. Instead, these findings are valuable primarily to help guide future research to better understand this disease and how to treat it.

Where does the study come from?

The study was done by researchers in Canada and the Netherlands, and it was funded by grants from several public and private research foundations.

What does this mean for me?

If you have MS, you may be concerned to learn that you have a risk factor associated with faster disease progression. But bear in mind that MS is an unpredictable illness and no one can say for certain what will happen to you. Indeed, being male or having early motor symptoms does not mean you will definitely develop secondary progressive MS more quickly. It just means that you have a higher chance of this happening than someone who doesn't have this risk factor. However, you may have other traits that actually lower your risk, such as taking immunomodulatory drugs.
What should I do now?

There's nothing you need to do based on this research. But be sure to talk to your doctor if you have any questions about your disease outlook and what steps you might take to stay healthy for longer.

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