Natural history of multiple sclerosis: risk factors and prognostic indicators

Sandra Vukusic[a,b,c,d] and Christian Confavreux[a,b,c,d]

Purpose of review

To highlight progress in the description of the natural course and prognosis of multiple sclerosis.

Recent findings

The general evolution of multiple sclerosis is now well known at the level of patient groups. Characteristics of relapses early in the disease and the occurrence of a progressive phase seemed to be the most reliable prognostic factors. Recent works suggest that the progressive phase in multiple sclerosis could be an age-dependent, degenerative process, independent of previous relapses, and that the initial course of the disease does not substantially influence age at disability milestones. By contrast, a younger age at disease onset strongly correlates with a younger age when reaching disability landmarks, confirming that even if it takes longer for younger patients to accumulate irreversible disability, they are disabled at a younger age than patients with later onset. Multiple sclerosis might be considered as one disease with different clinical phenotypes, rather than an entity encompassing several distinct diseases.

Summary

Overall course and prognosis in multiple sclerosis is most likely to be related to age and the occurrence of the progressive phase of the disease, rather than to relapses or other clinical parameters. Individual prognosis remains hazardous.

Keywords

disability, multiple sclerosis, natural history, prognosis

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[a]Service de Neurologie A and EDMUS Coordinating Center, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Lyon, [b]INSERM U 842, Lyon, [c]Université de Lyon, Lyon and [d]Université Lyon 1, Lyon, France

Correspondence to Dr Sandra Vukusic, Service de Neurologie A, Hôpital Neurologique Pierre Wertheimer, 59 Boulevard Pinel, 69677 Lyon Bron Cedex, France
Tel: +33 (0)4 72 68 13 10; fax: +33 (0)4 72 35 75 25;
e-mail: sandra.vukusic@chu-lyon.fr

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Abbreviations

CIS	clinically isolated syndrome
MRI	magnetic resonance imaging
MS	multiple sclerosis
PP-MS	primary progressive multiple sclerosis
RR-MS	relapsing–remitting multiple sclerosis
SAP-MS	single-attack progressive multiple sclerosis
SP-MS	secondary progressive multiple sclerosis

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Introduction

Prognosis remains one of the major challenges in multiple sclerosis (MS), for the patient as well as for the physician, despite considerable efforts concentrating for decades on the description of prognosis and its potentially influencing factors [1••]. Modern survival techniques allow us to consider not only patients who have reached the endpoints under study (death or, most frequently, irreversible disability), but also those who remain alive or not disabled at the date of their last visit, for the time they have been followed. Improvements in the quality and representativity of epidemiological studies have also led to a better knowledge of the prognosis, with prospective, population-based, natural history studies, and longitudinal and long-term follow-up [2,3].

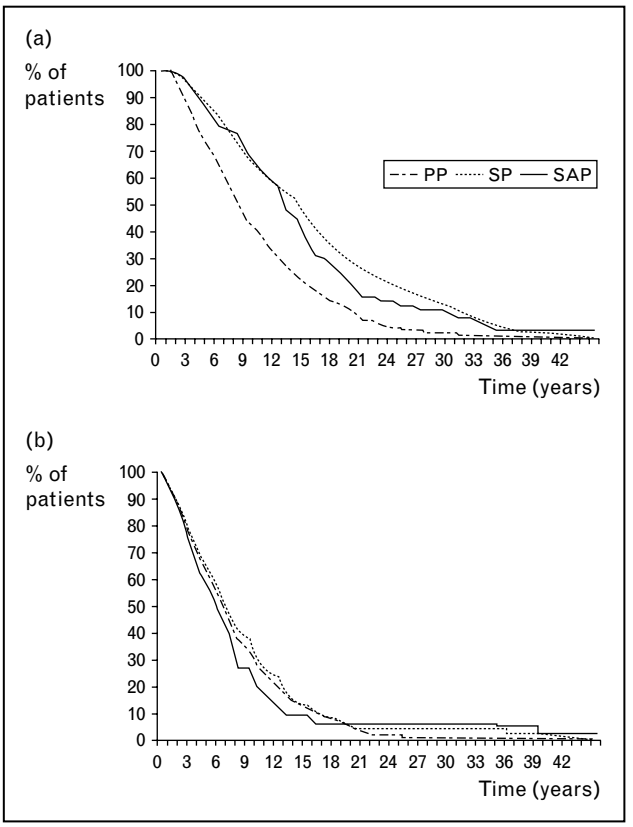
The general evolution of MS is well described among groups of patients and results are consistent among studies worldwide [1••], despite some recent reports of series with a better global prognosis [4,5,6•,7]. Thus, the median times to reach irreversible DSS 4 (limited walking ability but without aid or rest for more than 500 m), DSS 6 (ability to walk with unilateral support no more than 100 m without rest) and DSS 7 (ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support) are about 8, 20 and 30 years respectively. By contrast, the individual prognosis is still hazardous, and neither clinical data, conventional magnetic resonance imaging (MRI), nor biological markers are actually helpful for a specific case.

Relapses and progression as prognostic factors

Among the various prognostic factors, characteristics of relapses in the first years of the disease and the occurrence of a progressive phase seemed to be the most reliable. On one hand, it is well established that the evolution to an irreversible disability, whatever the score, takes longer in patients with an exacerbating–remitting onset, compared to those with a progressive one. The transition from a relapsing-remitting phase to a secondary progression is also associated with a worse evolution. On the other hand, factors related to relapses, as a monosymptomatic onset, with an optic neuritis, a complete recovery, a long time interval between the first and the second relapse, and a lower number of relapses within the first years, have consistently been associated with a better prognosis [1••,8].

However, these concepts have been debated in recent papers published at the same time by different teams. They questioned, in term of prognosis, the interplay between relapses and progression of disability. Kremenchutzky *et al.* [9••] explored once again the London, Ontario, MS database to examine the relationship between relapses, onset of the progressive phase and long-term disability accumulation. In two sets of patients they distinguished 219 patients with primary progressive MS (PP-MS), 140 with a single attack, followed at some time by progression (SAP-MS) and 817 with secondary progressive MS (SP-MS). These categories were chosen as they represented extremes in term of interaction between relapses and progression: from no relapse, to an isolated one, to many before the onset of progression. They showed that age at disease onset was different between groups (38.6, 33.3 and 29.8 years in PP-MS, SAP-MS and SP-MS), but conversely, that age at which progression begins was similar whatever the number of previous relapses (38.6, 40.9 and 39.2 years respectively). Furthermore, times from MS onset to disability landmarks were significantly longer in SAP-MS and SP-MS than in PP-MS patients, but times from onset of the progressive phase to disability landmarks were similar in the three groups (Fig. 1). They concluded that the progressive phase in MS could be an age-dependent, degenerative process, independent of previous relapses, whatever their number. Once progression has begun, its rate is largely independent of the past clinical history [10,11,12].

Figure 1 Time to DSS 6 from onset of multiple sclerosis (a) or onset of the progressive phase (b), among subgroups of patients with primary progressive (PP), single-attack progressive (SAP) and secondary progressive (SP) multiple sclerosis in the London, Ontario, cohort

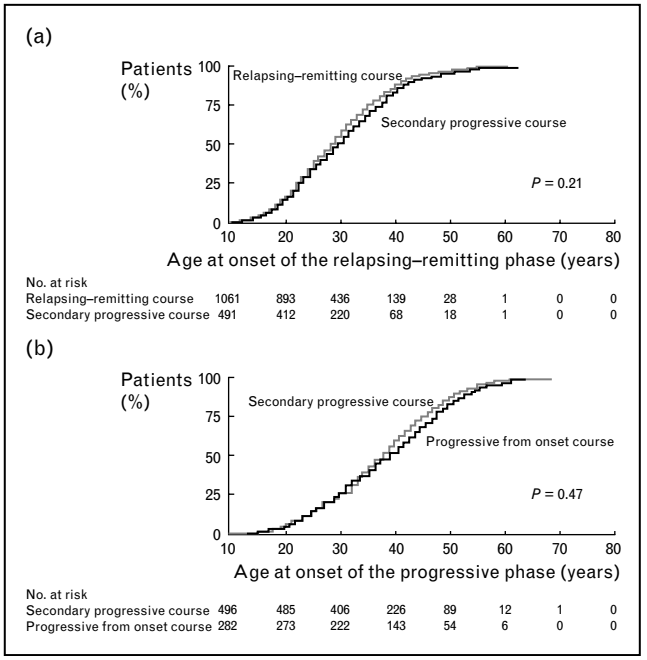


Adapted from [9••].

Interestingly, Confavreux and Vukusic [13••] reached similar conclusions from another perspective. Considering that all previous studies focused only on assessment of the times to reach disability milestones and not ages at which patients reach these landmarks, and that onset of the relapsing–remitting and the progressive phases have repeatedly been demonstrated to be age-related (Fig. 2) [14••], independently of the overall course of the disease, they decided to compare ages at which patients reach disability milestones according to their clinical course at the time of the study. They therefore analysed the 1844 patients from the Lyon MS database, an historical cohort set up in 1976. Patients with an exacerbating–remitting MS onset numbered 1562, whereas patients with a course that was progressive from onset were 282. Among the patients with an exacerbating–remitting initial course, 496 evolved later to secondary progression. Median ages at time to assignment of irreversible disability were 44.3 years for a score of DSS 4, 54.7 years for DSS 6 and 63.1 years for DSS 7. The initial course of the disease, whether exacerbating–remitting or progressive, had a statistically significant influence on ages at assignment of DSS 4 and DSS 6, but the differences were only marginal for the medians, with an overlap in the 95% confidence intervals. There was no difference with respect to assignment of DSS 7. Here is the place for some methodological considerations. When reaching disability landmarks, patients progressive from onset were younger than those with an exacerbating–remitting onset, but older than those with a secondary progressive course. The latter likely represent a select group of more rapidly worsening patients within the subgroup of exacerbating–remitting onset. Furthermore, the higher proportion of censored patients, not having experienced the endpoints – that is, irreversible disability – among patients with an exacerbating–remitting onset, could also contribute to the observed difference by overestimating the medians, compared to patients who were progressive from onset (Fig. 3). Therefore, the originality of this study is that it is the first to show that the initial course of the disease does not substantially influence age at disability milestones.

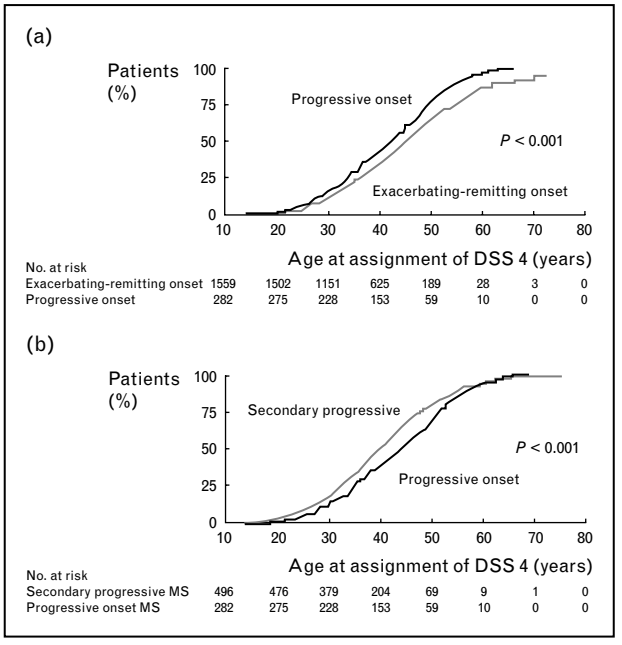
That said, another clinical factor is strongly and consistently associated with the time course of disability: age at MS onset. It is accepted that a younger age at onset is related to a slower disease progression and therefore a

Figure 2 Kaplan–Meier estimates for the age at onset of the relapsing–remitting phase (a) and the progressive phase (b) of multiple sclerosis in the Lyon, France, multiple sclerosis cohort



Adapted from [14••].

Figure 3 Kaplan–Meier estimates of the age at time of assignment of DSS 4 in subgroups of patients with an exacerbating–remitting or progressive onset (a) and patients with a secondary progressive course or progressive from onset (b), in the Lyon, France, multiple sclerosis (MS) cohort

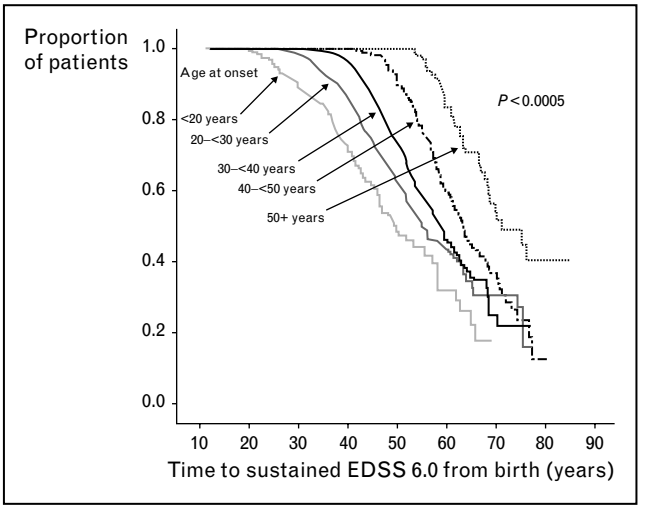


Adapted from [13••].

better prognosis. In the Lyon series, an earlier age at MS onset and a male gender, but not the initial symptoms, were associated with an earlier age at disability milestones, but not of the initial symptoms [13••]. Tremlett *et al*. [6•] have also given further evidence of the importance of current age. In 2837 patients followed at the University of British Columbia's MS clinic, they estimated the median time to an EDSS 6 to be 27.9 years, which is surprisingly longer than previous estimates in other series. The median age at which patients reached this endpoint was 59 years. There was no difference in ages at EDSS 6 between males and females, or according to initial symptoms. Patients with an exacerbating–remitting onset were significantly older when reaching EDSS 6 than those with a primary progressive course, but the difference was only 4 years. By contrast, a younger age at disease onset was strongly correlated with a younger age when reaching EDSS 6, confirming that even if it takes longer for younger patients to accumulate irreversible disability, they are disabled at a younger age and have to support longer the burden of the disease (Fig. 4). A younger age at MS onset should therefore no longer be considered as a good prognostic factor.

The clinical and epidemiological dissociation between relapses and disability accumulation in the long term is not contradictory with a short-term influence of relapses on MS course. It has been shown many times for example that the higher the number of relapses in the first years of the disease, the shorter the time from disease onset to assignment of irreversible disability scores [15]. However, this relationship seems to exist only before a detectable disability threshold has been reached. The same is true for other classically described early clinical

Figure 4 Kaplan–Meier survival curves of age at EDSS 6 according to age at onset of multiple sclerosis, in the University of British Columbia's cohort



Adapted from [6•].

predictors that were no longer associated with long-term outcome as estimated from DSS 4 or DSS 6 onwards [12,16]. It also has been clearly demonstrated that relapses do have an effect on the measure of short-term disability, which might be considered as confirmed in clinical trials if persisting over 3 or 6 months, but can surely not be considered irreversible as defined in natural history studies [17–19]. This point might be crucial, as strong assumptions have been made concerning correlations between relapse frequency and disability outcomes, and they have been influencial in determining clinical trial design and interpretation. Thus, the demonstration of a short-term effect (over a 2- or 3-year period) of immunoactive treatments on reducing the relapse rate and sometimes even disability outcomes has led to the potential of predicting a change in the long-term outcome of treated patients [20,21]. These recent results give new arguments against these hypotheses.

The currently acknowledged classification [22] describes the clinical course of MS with regard to the temporal interplay between relapses and progression, leading to separate relapsing–remitting, secondary progressive, primary progressive and progressive relapsing MS. It remains uncertain, however, whether these clinical phenotypes represent a heteregeneous but same disease, or underlie potentially different diseases. To debate this issue, Confavreux and Vukusic [14••] assessed demographic and clinical characteristics of their 1844 patients: 1066 had relapsing–remitting MS (RR-MS), 496 SP-MS, 109 were progressive–relapsing and 173 had PP-MS. Patients with a relapsing onset, be it RR-MS or SP-MS, shared similar ages at onset (28.5 and 29.5 years), initial symptoms, degree of recovery after the first relapse, and time between the first and the second episode. However, it has to be emphasized that disease duration was twice as long in SP-MS than in RR-MS. Similarly, patients with a progressive onset, with or without superimposed relapses, were comparable in their demographic and clinical characteristics. As for the onset of progression, median ages were similar in SP-MS and patients who were progressive from onset (39.1 and 40.1 years). The proportion of patients with superimposed relapses was about 40% in both subgroups. When comparing patients with an exacerbating–remitting course with those with a progressive onset, the study showed that they were essentially similar with respect to time course of disability accumulation from assignment to a given disability score, and with respect to the age at assignment of disability landmarks.

These observations suggest that the clinical phenotype and course of MS are mostly age-dependent, and lead the authors to speculate on a unifying concept of the disease, in which primary and secondary progression might be regarded as essentially similar. From a clinical and statistical position, MS might therefore be considered as one disease with different clinical phenotypes, rather than an entity encompassing several distinct diseases. RR-MS can be seen as MS in which insufficient time has elapsed for conversion to secondary progression to occur, SP-MS as RR-MS that has had time to grow older, and PP-MS as MS amputated from its usually preceding relapsing–remitting phase [1••,14••,20,23,24]. Therefore, the classification of MS course could be simplified as follows: onset is either exacerbating–remitting or progressive; the relapsing–remitting phase may be followed or not by a progressive phase; the progressive phase may be preceded or not by an exacerbating–remitting phase. Only three types of clinical course would remain: relapsing–remitting, secondary progressive and primary progressive, and the progressive phase may be superimposed with relapses or not [1••,14••,25].

All of these data are of course applicable only at the population level. It is a challenge now to develop individually predictive tools. Bergamaschi *et al.* [26•] very recently proposed an individual and simple clinical score that could be useful to detect patients likely to have a long-term bad prognosis. However, this score has to be validated on another set of patients to evaluate its predictive potential before it can be used in daily practice.

Clinically isolated syndromes

Prognosis can be considered from another point of view. In patients presenting for the first time with neurological symptoms suggesting an inflammatory demyelinating disease of the central nervous system, the crucial question is more likely to be diagnostic (do I have MS and when will I be sure of that?) than prognostic (will I become disabled and when?) [27]. Natural history studies can in part answer this question, but patients included in such studies might not be the same as those asking the question. It is for example classical to exclude patients in whom MS diagnosis is uncertain. Furthermore, these studies are interesting because they have a long follow-up duration, but conversely, this is often a reason why they do not have MRI data at baseline. It would today be difficult not to take account of MRI data. Studies of patients presenting with a clinically isolated syndrome (CIS) may therefore help. Some answers arose from immunoactive drugs trials after the first clinical episode [28–33], but they are unlikely to be representative of patients seen in daily practice, as their inclusion criteria were rather restrictive in terms of the severity of symptoms, time from onset to inclusion and, most of all, number of MRI lesions. Tintoré *et al.* [34] recently produced some useful information when studying 320 patients with CIS followed prospectively for a median of 39 months in an MS clinic in Barcelona, Spain. Inclusion criteria were somewhat less restrictive than trials, but excluded patients older than 50 and those seen more than

3 months after onset. CIS presentation was divided into optic neuritis, brainstem syndrome, myelitis, or other topography. Symptoms had to be suggestive of central-nervous-system demyelination not attribuable to another disease. MS was diagnosed either clinically, when there was a second attack with new neurological abnormalities confirmed by examination, or by MRI MacDonald criteria for dissemination in time and space on two scans acquired a year apart. Among the 320 patients, 72% were women, with a mean age at onset of 29.7 years. Isolated optic neuritis was overrepresented (38.4% of the patients) as compared to natural history series. The other presentations were brainstem syndrome in 24.4%, myelitis in 27.8% and other in 9.4%. Conversion to clinically definite MS was observed in 34.7% of the patients after a median of 14 months. It was not different according to gender and age at onset. It shows, however, that patients with optic neuritis have a smaller risk for converting to MS than patients with other CIS topographies. The authors also demonstrated that this observation was confounded by the results of MRI, and probably also of cerebrospinal fluid analysis. In fact, patients with optic neuritis had significantly fewer abnormal baseline MRIs (51 compared with 75–80%, respectively) and less often had cerebrospinal-fluid IgG oligoclonal bands (40 and 67–79%, respectively) than the others. When selecting only patients with abnormal MRI scans, prognosis was the same among all topographies. This is consistent with the well known fact that optic neuritis with normal MRI and cerebrospinal fluid analysis never converts to MS in a substantial proportion of cases [35]. This induced a bias towards a better prognosis of optic neuritis compared with other CIS topographies. The clue in the diagnosis and the occurrence of a second neurological episode seems then to be the normality of MRI rather than the clinical features.

Conclusion

The general evolution and prognosis of MS is well established in large natural-history series. Recent descriptions emphasize the fact that clinical phenotypes may be mainly age-related, and minimize the role of relapses in the long-term accumulation of disability. However, beyond this apparent global homogeneity in the clinical course, there is still a place for a very wide inter-individual heterogeneity, which is the reason why the individual profile remains largely unpredictable.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 366–367).

1 Confavreux C, Compston A. The natural history of multiple sclerosis. In:
•• Compston A, editor. McAlpine's multiple sclerosis, 4th edition. London: Churchill Livingstone Elsevier; 2006. pp. 183–272.
An exhaustive and up-to-date overview of the natural history of multiple sclerosis.

2 Ebers GC. Prognostic factors in multiple sclerosis: the importance of natural history studies. J Neurol 2005; 252:iii15–iii20.

3 Montalban X. The importance of long-term data in multiple sclerosis. J Neurol 2006; 253:vi9–vi15.

4 Pittock SJ, McClelland RL, Mayr WT, *et al.* Clinical implications of benign multiple sclerosis: a 20-year population-based follow-up study. Ann Neurol 2004; 56:303–306.

5 Pittock SJ, Mayr WT, McClelland RL, *et al.* Disability profile of MS did not change over 10 years in a population-based prevalence cohort. Neurology 2004; 62:601–606.

6 Tremlett H, Paty D, Devonshire V. Disability progression in multiple sclerosis is
• slower than previously reported. Neurology 2006; 66:172–177.
This study shows a better prognosis than previously reported, and emphasizes the role of age at onset as a prognostic factor.

7 Tremlett H, Paty D, Devonshire V. The natural history of primary progressive MS in British Columbia, Canada. Neurology 2005; 65:1919–1923.

8 Langer-Gould A, Popat RA, Huang SM, *et al.* Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. Arch Neurol 2006; 63:1686–1691.

9 Kremenchutzky M, Rice GP, Baskerville J, *et al.* The natural history of multiple
•• sclerosis: a geographically based study, 9: observations on the progressive phase of the disease. Brain 2006; 129:584–594.
An original design to demonstrate the lack of influence of previous relapses on accumulation of disability during the progressive phase of the disease.

10 Trojano M, Liguori M, Bosco Zimatore G, *et al.* Age-related disability in multiple sclerosis. Ann Neurol 2002; 51:475–480.

11 Confavreux C, Vukusic S, Moreau T, Adeleine P. Relapses and progression of disability in multiple sclerosis. N Engl J Med 2000; 343:1430–1438.

12 Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003; 126:770–782.

13 Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis.
•• Brain 2006; 129:595–605.
The clinical phenotype in MS is mainly an age-related process.

14 Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying
•• concept. Brain 2006; 129:606–616.
This paper compares the characteristics and course of the different clinical forms of MS, and gives arguments to consider that all these subtypes represent various phenotypes of the same disease.

15 Binquet C, Quantin C, Le Teuff G, *et al.* The prognostic value of initial relapses in the evolution of disability in patients with relapsing-remitting multiple sclerosis. Neuroepidemiology 2006; 27:45–54.

16 Vukusic S, Confavreux C. Prognostic factors for progression of disability in the secondary progressive phase of multiple sclerosis. J Neurol Sci 2003; 206:135–137.

17 Liu C, Blumhardt LD. Disability outcome measures in therapeutic trials of relapsing-remitting multiple sclerosis: effects of heterogeneity of disease course in placebo cohorts. J Neurol Neurosurg Psychiatry 2000; 68:450–457.

18 Rio J, Nos C, Tintoré M, *et al.* Assessment of different treatment failure criteria in a cohort of relapsing-remitting multiple sclerosis patients treated with interferon beta: implications for clinical trials. Ann Neurol 2002; 52:400–406.

19 Young PJ, Lederer C, Eder K, *et al.,* Sylvia Lawry Centre for Multiple Sclerosis Research. Relapses and subsequent worsening of disability in relapsing-remitting multiple sclerosis. Neurology 2006; 67:804–808.

20 Ebers GC. Disease evolution in multiple sclerosis. J Neurol 2006; 253:vi3–vi8.

21 Confavreux C, Vukusic S. Accumulation of irreversible disability in multiple sclerosis: from epidemiology to treatment. Clin Neurol Neurosurg 2006; 108:327–332.

22 Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. Neurology 1996; 46:907–911.

23 Vukusic S, Confavreux C. Primary and secondary progressive multiple sclerosis. J Neurol Sci 2003; 206:153–155.

24 Compston A. Making progress on the natural history of multiple sclerosis. Brain 2006; 129:561–563.

25 Confavreux C, Vukusic S. Natural history of multiple sclerosis: implications for counselling and therapy. Cur Opin Neurol 2002; 15:257–266.

26 Bergamaschi R, Quaglini S, Trojano M, *et al.* Early prediction of the long-term
• evolution of multiple sclerosis: the BREMS score. J Neurol Neurosurg Psychiatry 2007; Jan 12 [Epub ahead of print].
A step forward in defining an individual prediction tool, which has to be validated, however.

27 Miller D, Barkhof F, Montalban X, *et al.* Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis and prognosis. Lancet Neurol 2005; 4:281–288.

28 Beck RW, Trobe JD, Moke PS, *et al.,* Optic Neuritis Study Group. High- and low risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the Optic Neuritis Treatment Trial. Arch Ophthalmol 2003; 121:944–949.

29 Beck RW, Smith CH, Gal RL, *et al.,* Optic Neuritis Study Group. Neurologic impairment 10 years after optic neuritis. Arch Neurol 2004; 61:1386–1389.

30 Beck RW, Cleary PA, Trobe JD, *et al.* The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. The Optic Neuritis Study Group. N Engl J Med 1993; 329:1764–1769.

31 Jacobs LD, Beck RW, Simon JH, *et al.* Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 2000; 343:898–904.

32 Comi G, Filippi M, Barkhof F, *et al.* Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001; 357:1576–1586.

33 Kappos L, Polman CH, Freedman MS, *et al.* Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006; 67:1242–1249.

34 Tintoré M, Rovira A, Rio J, *et al.* Is optic neuritis more benign than other first attacks in multiple sclerosis. Ann Neurol 2005; 57:210–215.

35 Nilsson P, Larsson EM, Maly-Sundgren P, *et al.* Predicting the outcome of optic neuritis: evaluation of risk factors after 30 years of follow-up. J Neurol 2005; 252:396–402.