

Multiple Sclerosis That Is Progressive From the Time of Onset

Clinical Characteristics and Progression of Disability

P. B. Andersson, MBChB, DPhil; E. Waubant, MD; L. Gee, MPH; D. E. Goodkin, MD

Objective: To use the new consensus definitions of primary progressive multiple sclerosis (PPMS) and progressive relapsing multiple sclerosis (PRMS) to report the demographic, clinical, and natural history characteristics of multiple sclerosis (MS) that is progressive from the time of onset.

Design: Retrospective study by database/chart review and telephone interview.

Setting: Multiple sclerosis clinic at a university teaching hospital.

Patients: Eighty-three patients (prevalence, 6.9%) with PPMS and 12 patients (prevalence, 1.0%) with PRMS were studied.

Results: Fifty-nine percent of the patients with PPMS (n = 49) and 67% of the patients with PRMS (n = 8) were women. Mean \pm SD ages at the time of onset were 41.2 ± 10.5 and 38.0 ± 7.3 years, respectively; mean disease duration was 14.2 ± 8.8 and 12.2 ± 6.5 years,

respectively. The initial symptoms involved leg weakness in 94% of the patients with PPMS (n = 78) and 100% of the patients with PRMS (n = 12). For the PPMS cohort, a syndrome consistent with isolated myelopathy was found in 36% of patients (n = 30) and arm weakness without leg weakness did not occur. Mean \pm SEM time of progression to a score of 6.0 on the Expanded Disability Status Scale was 10.2 ± 1.0 years for patients with PPMS and 10.9 ± 2.6 years for patients with PRMS.

Conclusions: The clinical characteristics and disability progression of these MS subtypes were indistinguishable, with the exception of 1 or 2 relapses in patients with PRMS that occurred 8 months to 9 years after the onset of symptoms. We see little reason to consider PPMS and PRMS separate clinical entities; however, whether they can be better distinguished by radiological, histopathological, or immunological markers of disease activity remains unknown.

Arch Neurol. 1999;56:1138-1142

From the Mount Zion Multiple Sclerosis Center (Drs Andersson, Waubant, and Goodkin) and the Department of Biostatistics and Epidemiology (Ms Gee), University of California, San Francisco, School of Medicine.

IN 1996, an international survey was conducted to standardize multiple sclerosis (MS) disease course definitions. Consensus emerged¹ for the following terminology. *Relapsing-remitting MS* describes patients who experience an initial exacerbation followed by complete or incomplete recovery. Although approximately 85% of patients with MS have this disease course within 10 years of the initial attack, 50% develop a gradual progression of disability that may or may not be accompanied by exacerbations; this is called *secondary progressive MS*.²⁻⁴ Ten percent to 15% of patients experience a gradual progression of disability from the time of disease onset that is not accompanied by exacerbations⁵; this is called *primary progressive MS* (PPMS). Finally a new term, *progressive relapsing MS* (PRMS), was created to describe patients who experience MS that is progressive from the time of onset and is later accompanied by 1 or more relapses.

There are few studies that describe the characteristics of MS that is progressive from the time of onset,^{2-4,6,7} and just 1 article was published after the consensus definitions were proposed.⁷ Demographic and clinical characteristics for PPMS were given, but no natural history data were provided, nor was PPMS distinguished from PRMS. The purpose of this study was to apply the new definitions for MS that is progressive from the time of onset and report the natural history, demographic characteristics, and clinical characteristics seen at our tertiary referral center.

RESULTS

PRIMARY PROGRESSIVE MS

Diagnosis

Eighty-three (6.9%) of approximately 1200 patients in the clinic database met the con-

PATIENTS AND METHODS

PATIENTS

The study was approved by the University of California, San Francisco, Committee on Human Research. Medical records were reviewed for all patients who were seen at the University of California, San Francisco/Mount Zion Multiple Sclerosis Center from September 1993 through September 1996. Each patient completed a standardized neurological evaluation. Patients who met consensus criteria for PPMS or PRMS were selected for inclusion in this study.¹ All subjects were interviewed by telephone during a 2-week period with a standardized questionnaire to ascertain the progression of disability since the last clinic visit. When patients were too disabled to cooperate with the interview, a caregiver or close family member was interviewed.

STATISTICAL ANALYSIS

Sex differences for age, age at the time of first symptom, and disease duration were evaluated with the *t* test. Progression of the disease was evaluated as the time in years required to attain defined end points of disability. Associations between these end points and age at the time of symptom onset or disease duration were evaluated using the Cox proportional hazards model. Associations between level of disability and potential prognostic variables (ie, sex, clinical pattern of MS, impairment by functional system, and the number of impaired functional systems) were evaluated using nonparametric survival analysis stratified by levels of the prognostic factor. Evaluations of impairment by functional systems affected and the number of impaired functional systems were performed for the time of the first symptom and at years 1 through 5.

sensus definition for PPMS. Forty-three patients were diagnosed as having laboratory-supported definite MS (*n* = 28 for laboratory-supported definite MS B2; *n* = 15 for laboratory-supported definite MS B3),⁸ and 40 were diagnosed with clinically probable MS (*n* = 26 for clinically probable MS C2; *n* = 14 for clinically probable MS C3).⁸ Subjects with definite and probable MS were similar in sex distribution, age at the time of onset, duration of disease, and rate of progression of disability (data not shown).

Clinical Characteristics

Forty-nine (59%) of 83 patients with PPMS were women. The mean \pm SD disease duration from the time of the first symptom was 14.2 \pm 8.8 years (median, 12.2 years; range, 1.9-36.4 years). The mean \pm SD Expanded Disability Status Scale (EDSS) score at the time of the initial visit was 5.7 \pm 2.2 (median, 6; range, 1.5-9.5). The mean \pm SD age at the time of the first symptom was 41.2 \pm 10.5 years (me-

dian, 48 years; range, 17.4-69.4 years) (**Figure 1**). There was no relationship between sex and disease duration, EDSS score at the time of the initial visit, or age at the time of the first symptom.

Patients with PPMS experienced 1 or more symptoms at the time of disease onset. The most common initial symptom was weakness (59% [*n* = 49]). In 94% [*n* = 78] of these patients, weakness began in 1 leg and was commonly first detected by the patient only upon physical exertion. Cerebellar ataxia was an initial symptom for 24% (*n* = 20) of this cohort and generally affected the legs as gait imbalance in 85% (*n* = 71). Other initial symptoms were disturbances of sensation (paresthesias, numbness, or Lhermitte sign) (18% [*n* = 15]), blurred vision (7% [*n* = 6]), and urinary dysfunction (4% [*n* = 3]).

Neurological impairment at time of initial evaluation was categorized by affected Kurtzke functional systems^{9,10} (ie, pyramidal, *n* = 81 [98%]; bowel or bladder, *n* = 67 [81%]; cerebellar, *n* = 43 [51%]; sensory, *n* = 41 [49%]; vision, *n* = 34 [41%]; brainstem, *n* = 26 [31%]; and cognitive, *n* = 5 [6%]). Pyramidal functional system impairment (ie, limb weakness, spasticity, or hyperreflexia) was seen in the following patterns, typically with sparing of the facial musculature: in 1 leg (10% [*n* = 8]), in 1 arm (0% [*n* = 0]), in ipsilateral arm and leg (11% [*n* = 9]), in both legs (42% [*n* = 35]), in 3 limbs (11% [*n* = 9]), and in all limbs (26% [*n* = 22]). Thirty subjects (36%) had a syndrome consistent with an isolated myelopathy (ie, absence of ocular, brainstem, or cognitive abnormalities with pyramidal and/or sensory system involvement below the level of the medulla oblongata). Cognitive abnormalities were obvious during patient examination in 5 patients (6%). Neuropsychological testing for lesser degrees of cognitive impairment was not routinely performed as part of this study.

Cerebrospinal Fluid and Paraclinical Studies

Cerebrospinal fluid (CSF) analyses were performed on 54 subjects. Not all CSF parameters were tested on every subject. The white blood cell count ranged from 0 to 50 $\times 10^9$ /L and protein levels ranged from 0.41 to 0.89 g/L; 11% (*n* = 6) and 10% (*n* = 5) of subjects had abnormal white blood cell counts and protein levels, respectively. Oligoclonal bands or an elevated IgG index was found in 83% (*n* = 45) (**Table 1**). Brain and spinal cord magnetic resonance imaging (MRI) scans demonstrated a focal T₂-weighted signal consistent with MS in 88% (*n* = 73) and 47% (*n* = 39) of the subjects, respectively (Table 1). Among the 30 patients whose symptoms and signs at the time of the initial clinic evaluation were consistent with a myelopathy, 22 (85%) of 26 had abnormal brain MRI scans and 8 (42%) of 19 had spinal cord MRI scans consistent with MS. Twenty-six subjects completed at least 1 visual evoked potential, brainstem auditory evoked response, or somatosensory evoked response test; although the relative percentage of abnormally prolonged latencies varied from 50% for brainstem auditory evoked response to 68% for visual evoked potential, 85% (*n* = 22) had abnormally prolonged latencies.

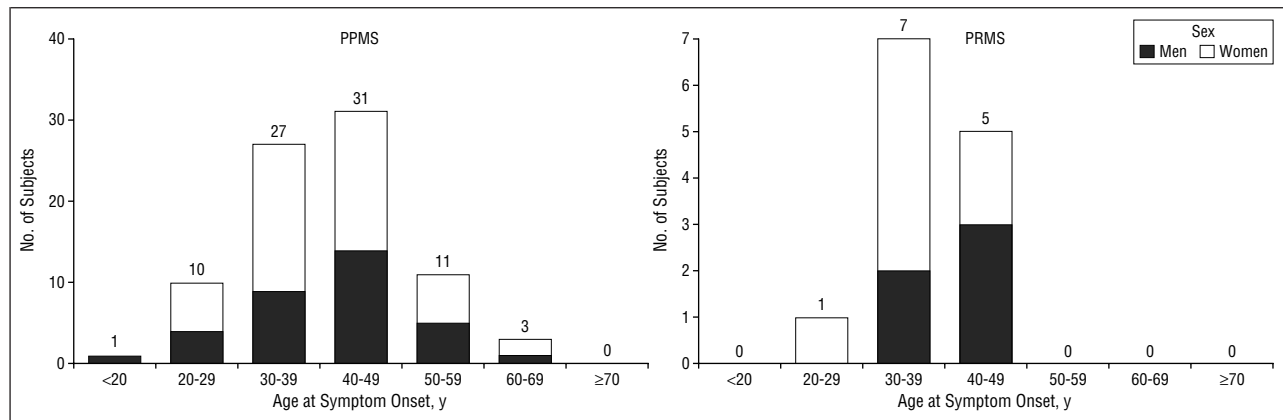


Figure 1. Age at the time of symptom onset for primary progressive multiple sclerosis (PPMS) and progressive relapsing multiple sclerosis (PRMS).

Table 1. Comparison of Subjects With Primary Progressive Multiple Sclerosis (PPMS) and Progressive Relapsing Multiple Sclerosis (PRMS) (N = 95)*

	Subjects With PPMS (n = 83)	Subjects With PRMS (n = 12)
Women, No. (%)	49 (59)	8 (67)
Age at onset of multiple sclerosis, y†	41.2 ± 10.5	38.0 ± 7.3
Leg weakness, No. (%)	78 (94)	12 (100)
Disease duration, y†	14.2 ± 8.8	12.2 ± 6.5
EDSS score at initial evaluation†	5.7 ± 2.2	5.0 ± 2.2
CSF oligoclonal bands or raised IgG index, No. (%)	45 (83)	5 (42)
Abnormal brain MRI, No. (%)	60 (88)	12 (100)
Abnormal cord MRI, No. (%)	21 (47)	4 (50)
Abnormal evoked potential, No. (%)	22 (85)	4 (50)
Time to progress to EDSS score of 6.0, y†	10.2 ± 1.0	10.9 ± 2.6

*EDSS indicates Expanded Disability Status Scale; CSF, cerebrospinal fluid; and MRI, magnetic resonance imaging.

†Values are mean ± SD.

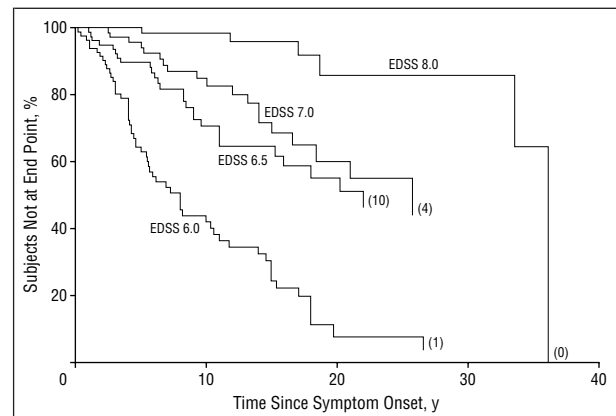


Figure 2. Survival analysis curves for progression of disability in patients with primary progressive multiple sclerosis. The times required to progress to the need for unilateral gait assistance (Expanded Disability Status Scale [EDSS] score, 6.0), bilateral gait assistance (EDSS score, 6.5), wheelchair use (EDSS score, 7.0), and the loss of the ability to transfer oneself independently to and from a wheelchair (EDSS score, 8.0) are given. The number of subjects remaining at the last data point is given in parentheses.

Progression of Disability

More than 96% of the patients with PPMS (n = 80) experienced difficulty walking after a mean disease duration of 1.1 years and 51% (n = 42) required unilateral gait assistance (EDSS score, 6.0) after 8 years (mean, 10.2 ± 1.1 years) (**Figure 2** and **Table 2**). The mean time required to progress from the need for unilateral gait assistance (EDSS score, 6.0) to the need for bilateral gait assistance (EDSS score, 6.5) was 7.8 years (median, 7 years). The mean time required to progress from the need for bilateral gait assistance to the need for wheelchair assistance (EDSS score, 7.0) was 4.5 years (median, 4 years; 95% confidence interval [CI], 2.2-5.7), and the mean time from the need for wheelchair assistance to the loss of the ability to transfer oneself independently to and from a wheelchair (EDSS score, 8.0) was 12.2 years (median, 10.4 years; 95% CI, 7.7-18.6). There were no differences in the times required to progress to these end points between patients with laboratory-supported definite PPMS or clinically probable PPMS (data not shown).

Predictors of Progression of Disability

The relationships among age, sex, disease duration, first affected functional system, number of first affected functional systems, and time required to reach EDSS scores of 6.0 and 6.5 were analyzed. Disease duration was correlated significantly with progression to EDSS scores of 6.0 (P = .008) and 6.5 (P = .04). The number of involved functional systems 3, 4, and 5 years after symptom onset was correlated with progression to EDSS scores of 6.0 and 6.5 (P = .02 for each), as was bowel and bladder involvement 4 and 5 years after the onset of the first symptom (P = .01 for each). There was no correlation between sex, age at the time of disease onset, first affected functional system, or number of affected functional systems at years 1 and 2 and time required to reach an EDSS score of 6.0 or 6.5.

PROGRESSIVE RELAPSING MS

Diagnosis

Twelve (1%) of approximately 1200 patients met the consensus definition for PRMS.¹ Ten were diagnosed

Table 2. Time to Progression to Various Levels of Disability in Subjects With Primary Progressive Multiple Sclerosis (N = 83)*

Impairment or Disability Level	No. of Subjects Reaching End Point	Disease Duration, y†
Abnormal gait	80	1.1 ± 0.03
Unilateral gait assistance required (EDSS score, 6.0)	57	10.2 ± 1.0
Urinary incontinence	43	15.3 ± 1.5
Bilateral gait assistance required (EDSS score, 6.5)	28	15.9 ± 1.0
Disabled from occupation	24	17.2 ± 1.1
Wheelchair use (EDSS score, 7.0)	19	19.8 ± 1.2
Loss of ability to live independently	14	27.7 ± 1.6
Loss of ability to transfer (EDSS score, 8.0)	6	32.6 ± 1.7

*EDSS indicates Expanded Disability Status Scale.

†Values are mean ± SEM.

as having clinically definite MS and 2 had laboratory-supported definite MS.⁸

Clinical Characteristics

Eight (67%) of the 12 patients with PRMS were women. The mean ± SD age at the time of the first symptom was 38.0 ± 7.3 years (median, 38.0 years; range, 23.0-49.5 years). The mean ± SD disease duration from the time of the first symptom was 12.2 ± 6.5 years (median, 11.2 years; range, 4.8-26.2 years). The mean ± SD EDSS score at the time of the initial visit was 5.0 ± 2.2 (median, 6.0; range, 0-7.0). There was no relationship between sex and disease duration, EDSS score at the time of the initial visit, or age at the time of the first symptom.

These patients with PRMS experienced 1 or more symptoms at the time of MS onset. All had leg symptoms initially, manifesting as weakness (31% [n = 4]), gait imbalance (38% [n = 5]), or numbness or paresthesias (38% [n = 5]). The mean ± SD time to the first exacerbation was 5.5 ± 3 years (range, 8 months to 9 years). The mean ± SD number of acute exacerbations was 1.6 ± 0.5. Five subjects experienced 1 exacerbation and 7 subjects experienced 2 exacerbations. None experienced more than 2 exacerbations. The exacerbations manifested as isolated optic neuritis in 9 patients, optic neuritis with limb paresis in 1, isolated diplopia in 2, diplopia with limb weakness in 1, limb paresis in 3, limb paresis and sensory loss in 1, and isolated limb sensory loss in 2. At the time of the first evaluation at the clinic, the location and frequency of functional system involvement was pyramidal (92% [n = 11]), bowel and bladder (75% [n = 9]), cerebellar (58% [n = 7]), sensory (42% [n = 5]), visual (25% [n = 3]), brainstem (25% [n = 3]), and cognitive (0%).

CSF and Paraclinical Testing

Eleven subjects had an abnormal brain MRI scan and 2 subjects had an abnormal spinal cord MRI scan. Two of 5 subjects had CSF oligoclonal bands or an elevated CSF IgG index.

Progression of Disability and Predictors of Progression of Disability

Seven of the 12 patients reached an EDSS score of 6.0 after 10.9 ± 2.6 years (mean ± SEM), which was not different from patients with PPMS ($P = .45$). The meaningful assessment of the time required to reach EDSS scores of 6.5, 7.0, and 8.0 or predictors of disease progression was prevented by the small sample size.

COMMENT

In summary, with the exception of 1 or 2 relapses experienced 8 months to 9 years after symptom onset, we could not distinguish PRMS from PPMS. We therefore see little reason to consider them separate clinical entities. This study extends previous observations in patients with PPMS^{3,4,6,7,11} and provides the first detailed description of demographic features, clinical characteristics, and natural history of patients with PRMS. The prevalence of PPMS in our cohort was 6.9%, lower than that of previous reports (range, 9%-37%).^{2-4,12} Our observations of a 1% PRMS prevalence with rare relapses that were generally not experienced until several years after symptom onset differs markedly from the large retrospective population-based study of Weinshenker et al,^{3,11} who reported a prevalence of 14.8% and a relapse rate of 0.48 during the first 2 years of disease. It is not clear to what extent these differences reflect differences in interpretation of initial symptoms, referral patterns, or genetic heterogeneity.¹³ The mean age of symptom onset for both PPMS and PRMS in our study is older than that previously reported for relapsing-remitting patients.^{2,14} It remains unclear whether MS that is progressive from onset represents one end of a broad spectrum of a single disease or whether it is another disease altogether. The latter hypothesis is supported by evidence that PPMS can be distinguished clinically,^{1,15} histopathologically,¹⁶ radiologically,¹⁷ and by immunologic markers¹⁸ from relapsing-remitting MS.

Almost all subjects with PPMS and PRMS experienced leg weakness or gait unsteadiness. In contrast, isolated pyramidal findings in the arms were never observed and facial musculature was typically spared when limbs were affected. This pattern of pyramidal findings differs from that observed in relapsing-remitting MS. A presentation compatible with a myelopathy was seen in more than one third of the PPMS cohort. This proportion would have risen to 54% if uncorrectable mild visual impairment or the presence of optic disc pallor had been ignored. Evidence of disseminated lesions on brain MRI scans was present in more than 80% of subjects with a purely myelopathic presentation. These observations underscore the importance of a careful ocular examination and brain imaging¹⁹ in the evaluation of myelopathy that is not attributable to spinal cord compression.

There are 4 studies that describe progression of disability in PPMS. Minderhoud et al² observed that 7.4% of 128 patients progressed to an EDSS score of 7.0 within 5 years, 30.6% within 15 years, and 62.2% within 25 years. Troiano et al⁶ observed that 53% (n = 32) of 60 patients

progressed to or beyond an EDSS score of 6.0 within 10 years of disease onset, and median times required to progress to an EDSS score of 6.0 have been reported as 4.5 years in a cohort of 205³ and 6 years in a cohort of 36.⁴ Progression rates in PRMS have not been reported. We observed that 71% (n = 59) of 83 subjects with PPMS and 58% (n = 7) of 12 subjects with PRMS reached an EDSS score of 6.0 after a similar mean disease duration of 10.2 and 10.9 years, respectively ($P = .45$). The median time required for our PPMS cohort to reach an EDSS score of 6.0 was longer (8 years) than the 4.5 years observed by Weinshenker et al.³ The reason for this difference is unclear but may reflect different definitions for an EDSS score of 6.0. We defined an EDSS score of 6.0 as the point where a cane was required for ambulation. Since many patients with MS walk with a cane well before it is required, our definition may have extended the time for patients in our cohort to reach an EDSS score of 6.0.

The limitations of our study are similar to those of earlier reports. With the exception of 19 patients observed by Weinshenker et al.³ from disease onset, all were retrospective. Thus, data are largely based on chart review and patient interviews that are subject to considerable interpretation. The possibility that disease-modifying treatments may have delayed the progression of disability needs to be considered. The number of patients receiving immunosuppressive treatments in other studies was not reported.^{2-4,6} Ten subjects in our cohort were treated with methotrexate, 7.5 mg orally each week for up to 1 year, and no patient received azathioprine or cyclophosphamide. We believe it is unlikely that methotrexate therapy significantly affected our study because efficacy in delaying disease progression has not been demonstrated for PPMS.²⁰

Allowing for differences in method, studies of patients with MS that is progressive from onset provide a consistent message. The clinical presentation is generally leg weakness, and most patients experience gradually progressive leg weakness, gait instability, and bladder dysfunction. Our data indicate that isolated upper-extremity weakness does not occur and facial muscles are generally not affected in PPMS. Fifty percent of patients with PPMS will require unilateral assistance to ambulate approximately 8 years after the appearance of initial symptoms. With the exception of 1 or 2 superimposed relapses generally experienced several years after the gradual onset of symptoms, the clinical presentation and natural history of PPMS and PRMS are indistinguishable.

Accepted for publication December 8, 1998.

Corresponding author: D. E. Goodkin, MD, Mount Zion Multiple Sclerosis Center, University of California, San Francisco School of Medicine, 1701 Divisadero St, Suite 480, San Francisco, CA 94115-1642 (e-mail: goodkin@mscenter.his.ucsf.edu).

REFERENCES

1. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology*. 1996;46:907-911.
2. Minderhoud JM, van der Hoeven JH, Prange AJA. Course and prognosis of chronic progressive multiple sclerosis: results of an epidemiological study. *Acta Neurol Scand*. 1988;78:10-15.
3. Weinshenker BG, Bass B, Rice GPA, et al. The natural history of multiple sclerosis: a geographically based study, 1: clinical course and disability. *Brain*. 1989;112:133-146.
4. Runmarker B, Andersen O. Prognostic factors in a multiple sclerosis incidence cohort with twenty-five years of follow-up. *Brain*. 1993;116:117-134.
5. Thompson AJ, Polman CH, Miller DH, et al. Primary progressive multiple sclerosis. *Brain*. 1997;120:1085-1096.
6. Troiano M, Avolio C, Manzari C, et al. Multivariate analysis of predictive factors of multiple sclerosis course with a validated method to assess clinical events. *J Neurol Neurosurg Psychiatry*. 1995;58:300-306.
7. McDonnell GV, Hawkins SA. Clinical study of primary progressive multiple sclerosis in Northern Ireland, UK. *J Neurol Neurosurg Psychiatry*. 1998;64:451-454.
8. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol*. 1983;13:227-231.
9. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444-1452.
10. Goodkin DE. Multiple sclerosis: clinical design for the future. *Mult Scler*. 1996;1:393-399.
11. Weinshenker BG, Bass B, Rice GPA, et al. The natural history of multiple sclerosis: a geographically based study, 2: predictive value of the early clinical course. *Brain*. 1989;112:1419-1428.
12. Phadke JG. Clinical aspects of multiple sclerosis in northeast Scotland with particular reference to its course and prognosis. *Brain*. 1990;113:1597-1628.
13. Multiple Sclerosis Genetics Group. Clinical demographics of multiplex families with multiple sclerosis. *Ann Neurol*. 1998;43:530-534.
14. Goodkin DE, Hertsgaard D, Rudick RA. Exacerbation rates and adherence to disease type in a prospectively followed up population with multiple sclerosis. *Arch Neurol*. 1989;46:1107-1112.
15. Comi G, Filippi M, Martinelli V, et al. Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. *J Neurol Sci*. 1995;132:222-227.
16. Revesz T, Kidd D, Thompson AJ, Barnard RO, McDonald WI. A comparison of the pathology of primary and secondary progressive multiple sclerosis. *Brain*. 1994;117:759-765.
17. Thompson AJ, Kermode AG, Wicks D, et al. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Ann Neurol*. 1991;29:53-62.
18. Giovanni G, Thorpe JW, Kidd D, et al. Soluble E-selectin in multiple sclerosis: raised concentrations in patients with primary progressive disease. *J Neurol Neurosurg Psychiatry*. 1996;60:20-26.
19. Filippi M, Martinelli V, Locatelli T, et al. Acute- and insidious-onset myelopathy of undetermined aetiology: contribution of paraclinical tests to the diagnosis of multiple sclerosis. *J Neurol*. 1990;237:171-176.
20. Goodkin DE, Rudick RA, VanderBrug Medendorp S, et al. Low-dose (7.5 mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. *Ann Neurol*. 1995;37:30-40.