Multiple Sclerosis—From Probable to Definite Diagnosis

A 7-Year Prospective Study

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Objectives: To investigate the rate of progression from probable to clinically definite multiple sclerosis (MS) and to define patients who had rapidly (within 1 year) progressed to a definite diagnosis.

Design: A 7-year prospective study.

Patients: A group of 163 patients experiencing their first episode of neurologic symptoms suggestive of MS. All patients had brain magnetic resonance imaging that demonstrated at least 3 demyelinating lesions at onset.

Results: Within the follow-up period (mean, 42 months; range, 13-84 months), 136 patients (83.4%) had an additional relapse and were thus defined as having clinically definite MS, whereas 27 patients (16.6%) were defined as having clinically probable MS. Most of the 136 patients with clinically definite MS (57.6%, 94 patients) experienced the additional relapse within 1 year. Demographic and clinical parameters at presentation were analyzed to identify variables predictive of rapid progression (within 1 year) to clinical definite MS. Motor involvement at onset was the only clinical parameter associated with rapid progression to a definite diagnosis. Survival curves demonstrated that polysymptomatic involvement and higher Extended Disability Status Scale score at presentation correlated with rapid progression to definite diagnosis.

Conclusion: Most patients with a diagnosis of probable MS and positive brain magnetic resonance imaging will progress rapidly to clinically definite MS.

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T he first appearance of various combinations of motor, sensory, coordination, visual, and cognitive impairments, as well as symptoms of fatigue and urinary tract dysfunction compatible with central nervous system (CNS) involvement in young patients, raises the possibility of multiple sclerosis (MS). The gradual resolution of these symptoms during a period of days to weeks further supports this diagnostic entity. In the last decade, extensive use of electrophysiologic studies, brain and spinal cord imaging, and immunologic parameters has contributed immensely to early diagnosis of MS. However, the diagnostic algorithm still requires that definite MS be clinically diagnosed only when the second neurologic relapse occurs. Thus, between the first and second relapse, patients are classified as having probable MS.

This seemingly subtle phenomenologic difference may, in fact, be a critical period in which the immunologic processes underlying the disease are awaiting our clinical confirmation. Moreover, several recent studies have emphasized the importance of epitope spreading in uncovering additional sites for autoimmune attack. The process of epitope spreading is one in which immune tolerance to a component of a macromolecular particle is followed by diversification of additional components through recognition of new epitopes within the particle. Lehmann et al demonstrated that cryptic myelin basic protein determinants become immunogenic following primary immunization. In concert with other authors, they suggest that the “prevention of second-wave priming to autoantigens might be a prerequisite for successful therapy.” Therapeutic intervention immediately after onset of the autoimmune process may be of particular importance in patients with the first episode of a demyelinating syndrome at high risk.
**PATIENTS AND METHODS**

For the purpose of the present study the following definitions were used.

**Clinical probable MS** was defined as onset of new neurologic symptoms, predominantly white matter involvement, occurring for at least 48 hours and resolving partially or completely within 2 to 8 weeks (ie, attack), with clinical evidence of at least 1 lesion producing objective CNS dysfunction and with paraclinical evidence of demyelinating lesions by brain MRI examination (positive brain MRI) (CPMS C2 or CPMS C3).14

**Clinical definite MS** was defined as 2 attacks with clinical evidence of 2 separate lesions, with at least 1 of these lesions producing objective CNS dysfunction and with paraclinical evidence of demyelinating lesions by brain MRI examination (CDMS A1 or CDMS A2).14

**Positive brain MRI** was defined as the appearance of 3 or more ellipsoid demyelinating lesions whose diameter is 3 mm or more within the brain. Of these lesions, at least 1 is evident within the periventricular white matter or brainstem in a diameter of 6 mm or longer.15

**Rapid progression** was defined as occurrence of a second attack within 1 year following the first relapse.

In all cases, duration to the second relapse was counted following 30 days of partial or complete remission following the onset of the first attack. Accordingly, we categorized 2 groups for the purpose of statistical comparison: a group of patients with rapid progression (RP), ie, patients with clinically probable MS who experienced additional relapse within 1 year, and a second group with slower progression (SP), ie, patients who developed definite MS after more than 1 year.

**PATIENTS**

The Neuroimmunology Unit at the Sheba Medical Center, Tel-Hashomer, Israel, serves as a medical facility for the diagnosis, treatment, and rehabilitation of patients with MS. At present, the unit provides services for 776 patients with MS. From January 1991 to December 1997, all patients presenting with probable MS were enrolled in the study. Each patient was followed up systematically and examined neurologically every 3 to 6 months. Only patients with a follow-up of at least 12 months were included in the final analysis. At a time of suspected relapse, an additional examination was performed. When a diagnosis of a second relapse was established, the patient was defined as having clinically definite MS, and all related data were transferred to a new computerized data file until final analysis. Patients with primary progressive course were excluded. All patients underwent brain MRI performed on a 0.5-T superconductive magnet system (Gyrex V, Elscint, Israel). Spin echo T1-weighted scans were obtained in the sagittal plane with a repetition time of 400 to 600 milliseconds and time to echo of 20 milliseconds. Spin echo proton density and T2-weighted sequences were performed using a repetition time of 3000 milliseconds, a time to echo of 20 and 80 milliseconds, a 5-mm slice thickness, and a 1-mm gap between slices. All scans were interpreted by a neuroradiologist. In all patients, a thorough workup to exclude other possible diagnostic entities, such as collagen diseases, B12 deficiency, human T-lymphotropic virus type 1 infection, cervical spondylosis, and craniovertebral anomalies, was performed. Neurologic disability was evaluated by the Extended Disability Status Scale (EDSS).13 The EDSS is an 8-item functional system scale that includes motor, sensory, cerebellar, brainstem, visual, mental, sphincteric, and other systems. Each system is graded from 0 (no disability) to 5 or 6 (maximal disability). According to the score in each functional system, an integrated score between 0 (normal examination) and 10 (death from MS) is derived. An EDSS score of 6.0 indicates walking with assistance for a distance of 100 m. Exacerbation severity was graded as follows: (1) mild—change in 1 grade in the score for 1 of the 8 functional scores of the Kurtzke EDSS; (2) moderate—change in 2 grades in the score for 1 of the 8 functional scores of the EDSS or change in 1 grade in the score for 2 of the 8 functional groups; or (3) severe—change in 2 grades in the score for at least 2 of the 8 functional scores of the EDSS. Severe exacerbations only with polysymptomatic functional involvement (n=44) were treated with intravenous methylprednisolone sodium succinate (1 g/d) for 5 consecutive days.

**STATISTICAL METHODS**

Differences in proportions were tested for significance using the Pearson χ2 and the Fisher exact tests, with a 2-tailed level of significance. Univariate analysis was performed for age, sex, steroid (methylprednisolone sodium succinate) treatment during the first relapse, monosymptomatic or polysymptomatic involvement at onset, and EDSS score. Multivariate analysis was performed for relapse severity and functional system scores. Spearman correlation was applied for testing the correlation between the clinical and demographic parameters. Cox proportional hazards models, with and without time-dependent covariates, were used to analyze the relation between neurologic symptoms and time to second relapse. Calculations were performed using the PROC PHREG program with SAS statistical software, version 6.09 (SAS Institute Inc, Cary, NC). All tests were 2-tailed, and P<.05 was considered statistically significant. Results are expressed as mean ± SD.
From 1991 to 1997, a group of 198 patients experiencing their first episode of neurologic symptoms suggestive of MS were included in the first evaluation. A total of 172 patients who also had a positive brain MRI fulfilling the criteria of clinically probable disease were included in the study. During the follow-up period, 9 patients (5.2%) were lost to follow-up (Figure 1). Of the remaining 163 patients (115 women, 48 men; female-male ratio of 2.4:1), 136 (83.4%) experienced at least 1 additional relapse and were thus classified as having definite MS. Twenty-seven patients (16.6%) remained in the clinically probable disease group during a mean follow-up period of 42 months (range, 13-84 months) (Figure 2). Ninety-four patients (57.6%) relapsed within the first year of being diagnosed as having probable MS, and these patients comprised the RP group. This magnitude of RP held true not only for the total 7 years but also for each calendar year. One hundred thirty patients (79.7%) had reached a definite diagnosis of MS within 3 years. The clinical and demographic data of the patients are presented in the Table. Age at first relapse and sex did not differ between groups. Neurologic disability at onset evaluated by the EDSS score did not differ between the RP and SP groups (P=.52, Table). Similarly, involvement of any one of the functional systems (score >0) of the EDSS did not discriminate between the RP and SP groups at onset. Only pyramidal involvement at onset, which was significantly higher in the RP group (Fisher exact test, P=.03), differentiated between the 2 groups. The majority of patients in the present series (62.5%, 85/136) had a monosymptomatic presentation at onset. Demographic and clinical characteristics of the 27 patients who had remained in the probable MS group throughout the study are also presented in the Table. This group of patients did not differ significantly from the other 2 groups except for the overpresentation of visual involvement (40.7% vs 23.2% and 21.0%; Fisher exact test, P=.02).

Corticosteroid treatment during the first relapse was not associated with slower progression to clinically definite diagnosis. Patients treated with steroids (n=44) demonstrated a mean time to the second relapse of 1.2 years (95% confidence interval, 0.86-1.55), whereas untreated patients showed a mean time to the second relapse of 1.4 years (95% confidence interval, 1.20-1.62).

Survival curves for a patient to remain in the probable MS group or experience an additional relapse over time are presented in Figure 3. Survival distributions between groups in relation to neurologic disability by EDSS score are presented in Figure 4, and Figure 5 presents the survival distributions between groups in relation to monosymptomatic or polysymptomatic neurologic involvement at onset. The presentation of polysymptomatic involvement and higher EDSS score suggestive of more severe neurologic involvement at onset were significant risk factors for developing definite MS within 1 year.

A definitive diagnosis of MS cannot be made at presentation, since dissemination in time is not established. The correct identification of patients with very early MS who carry a high risk of progression to clinically definite MS is of the utmost importance, because in the last decade new treatment modalities emerged that have been proven to reduce relapse frequency.

Theoretically, these disease course-modifying agents may have a role in the prevention or slowing of the process, leading to full-blown MS. Munschauer and Stuart have recently argued that the disease-modifying therapies now available have changed our outlook on the treatment of MS from being merely symptomatic to active intervention against disease activity. Although at present the ability to modify the disease course of MS is still limited, evidence from both basic neuroscience research and clinical trials supports the rationale that therapy should be initiated as early as possible during the disease. In addition, brain MRI studies have provided us with evidence that in patients with MS CNS inflammation progresses even without overt clinical symptoms, further underlining the need to resolve the question “when should treatment be initiated?” Although they do not di-
directly answer this question, both the Optic Neuritis Study Group and the guidelines for early treatment of patients at high risk for conversion to MS suggest that the administration of steroid therapy immediately after the first attack delays the occurrence of subsequent signs and/or symptoms, thus delaying the progression to clinically definite MS.

In the present study, steroid treatment during the first relapse was not associated with delay of progression to clinically definite MS. This may be related to the fact that we have included in our series patients with positive MRI and steroid treatment was initiated only in cases of severe relapses with polysymptomatic involvement. This subpopulation of patients more closely corresponds to the adjusted rate ratio of 5.53 in patients with 3 or more lesions in brain MRI progressing to clinically definite MS, as reported by the Optic Neuritis Study Group.

In the present study, we aimed to identify patients with probable MS at high risk of progressing to clinically definite MS within a period of 1 year (the RP group) and assess the predictive value of clinical and demographic parameters at onset for the development of definite MS. We found that 57.6% of patients experienced a relapse within this period. Our findings may be compared with both historical studies and recent research that focuses on the course of isolated syndromes of the CNS, especially optic neuritis. In the early
studies, rates of conversion within the first year of onset ranged from 25% in McAlpine’s19 and Muller’s20 series to a rate as high as 41.2% reported by Adams et al.21 These studies were mainly retrospective and based on clinical findings, whereas the advent of brain MRI has allowed further data to emerge. In recent studies, the progression to clinically definite MS in patients with an abnormal brain MRI was 49% and 65% in the first 5 years,22-25 41% and 68% within 2 years,24,26 and 24% and 45% within 1 year.17,23 In all these studies, the predictive value of at least 3 disseminated white matter lesions on brain MRI at onset was highly significant. It should be stressed that in our series 36.2% of patients had a polysymptomatic presentation and not only isolated neurologic involvement, probably contributing to the higher rate of conversion to clinically definite MS compared with other studies. Severity of neurologic disability and polysymptomatic functional system involvement at onset were associated with significant risk of subsequent development of definite MS. It can be assumed that the appearance of polysymptomatic clinical presentation and higher EDSS scores are reflecting disseminated white matter disease comparable to the positive brain MRI. This is also supported by the disproportionate distribution of patients in the RP group within the polysymptomatic vs monosymptomatic presentations. In addition, many patients whose condition had not converted to definite MS were characterized by involvement at presentation of the visual system only. This finding, supported by other authors,17 underlines the importance of limited CNS involvement, which is associated with better prognosis.

Our findings essentially do not propose a difference in demographic, clinical, and treatment (steroid therapy at onset) variables between patients with rapidly progressive disease and patients with SP disease. Only pyramidal involvement at onset was associated with rapid progression to definite MS. The involvement of the motor system has been reported by other authors to be related to a rapid progression to disability.27-29 These data indicate that individuals at high risk for definite MS may be identified by the severity and multiplicity of neurologic symptoms at onset. The prognostic usefulness of these clinical measurements, relatively early in the natural history of MS, may be important to characterize patients who will rapidly reach definite diagnosis. The relatively high proportion of such patients calls for a change in the early management of probable MS. The advent of novel immune-modulating drugs that affect the course of MS transports the findings of the present study from the realm of theoretical implications to clinical decision making. Moreover, the development of MS is accompanied by increasing recognition of new self-determinants of encephalitogenic peptides released during the primary process of tissue damage. Several lines of evidence demonstrate that this phenomenon of epitope spreading is pathogenic for disease progression and a relationship exists between additional relapses and the spreading of recognition to new determinants. Taken together these data make a strong case for early therapeutic interventions after onset of the autoimmune disease process.7-30,31 We suggest that therapy be started immediately after the first attack to reduce the rate of progression to clinically definite MS. This should be evaluated in clinical trials so that patients with MS still in the probable category benefit from the disease course-modulating effects of available therapeutic treatments.

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