Clinical Implications of Benign Multiple Sclerosis: A 20-Year Population-Based Follow-up Study

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In 2001, we followed up all patients from the 1991 Olmsted County Multiple Sclerosis (MS) prevalence cohort. We found that the longer the duration of MS and the lower the disability, the more likely a patient is to remain stable and not progress. This is particularly powerful for patients with benign MS with Expanded Disability Status Scale score of 2 or lower for 10 years or longer who have a greater than 90% chance of remaining stable. This is important because these patients represent 17% of the entire prevalence cohort. These data should assist in the shared therapeutic decision-making process of whether to start immunomodulatory medications.

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The use of immunomodulatory drugs in patients with multiple sclerosis (MS) or a clinically isolated syndrome and a magnetic resonance image suggestive of MS is drastically increasing in the United States.[1–4] The term *benign MS* has been used in the past to describe MS patients that are doing well.[5–11] Regardless of the definition used, the question as to whether these patients should be treated with immunomodulatory therapies remains.

We previously reported the functional status of all 1991 prevalence cases (n = 162) of MS in Olmsted County and subsequently published a 10-year follow-up study on the same cohort.[8,12] In this study, we focus on patients considered benign (Expanded Disability Status Scale [EDSS] score $\leq$4, duration $>$10 years) in 1991 and report their level of disability an additional 10 years later (minimal disease duration $>$20 years).[8] We investigated the level of disability and duration of disease as predictors of subsequent EDSS 10 years later.

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Patients and Methods

Patients from the 1991 prevalence cohort were rescored (by S.J.P. or W.T.M.) in 2001 using the Minimal Record of Disability (MRD) with the investigators blinded as to the 1991 EDSS scores.[8,12,14,15] Patients were required to be at these specific EDSS scores for at least 6 months.

We recorded the following information from the patient and/or review of the clinical record: onset age, onset neurological symptoms (type, mono vs polyregional, degree of recovery), number of attacks in the first 2 years, use of immunomodulatory drugs, duration of MS, course (relapsing-remitting [RR], secondary-progressive [SP], or primary progressive [PP]) and quality of life (QOL) on a scale of 0 to 10, with 0 being worse than death and 10 being the best that one could imagine. RR patients who had progression of disability in between attacks or who developed progressive disability without further attacks were characterized SPMS. For patients who died, we reviewed death certificates and used the neurological examination recorded in the year before death to approximate the EDSS.

Logistic regression models were used to evaluate associations between patient characteristics and a benign disease course. Unadjusted odds ratios, 95% confidence intervals, and p values were calculated for each variable. A stepwise multiple logistic regression model was constructed with p value less than 0.10 required for entry at each step.

Results

The classification of patients is shown in Figure 1. In 1991, 49 patients were considered benign, and 47 were alive in 2001; 43 were examined and 4 had a telephone interview. The change in EDSS over 10 years is shown in Figure 2. No patients with EDSS 4 or lower after at least 20 years had received immunomodulatory medications (β-interferon or glatiramer acetate).

Impact of Duration of Disease from Onset on Disability

For patients with EDSS 2 or lower or EDSS 2.5 to 4 in 1991, we studied the effect of duration of disease from onset on further change in EDSS 10 years later (Table). In 1991, 53 of 162 patients had EDSS score of 2 or lower. Four (29%) of 14 patients with EDSS score of 2 or lower and duration of up to 5 years in 1991 developed significant disability (EDSS $\geq$6, all were actually wheelchair-bound or worse) 10 years later. In contrast, none of 39 patients with EDSS score of 2 or lower and duration of longer than 5 years in 1991 became wheelchair-bound, and only one required a cane to walk. In contrast, 10 of 27 (37%) patients with EDSS 2.5 to 4 for longer than 5 years in 1991 had an EDSS score higher than 6, when evaluated a decade later (see Table).

Patients with EDSS score of 2 or lower for longer

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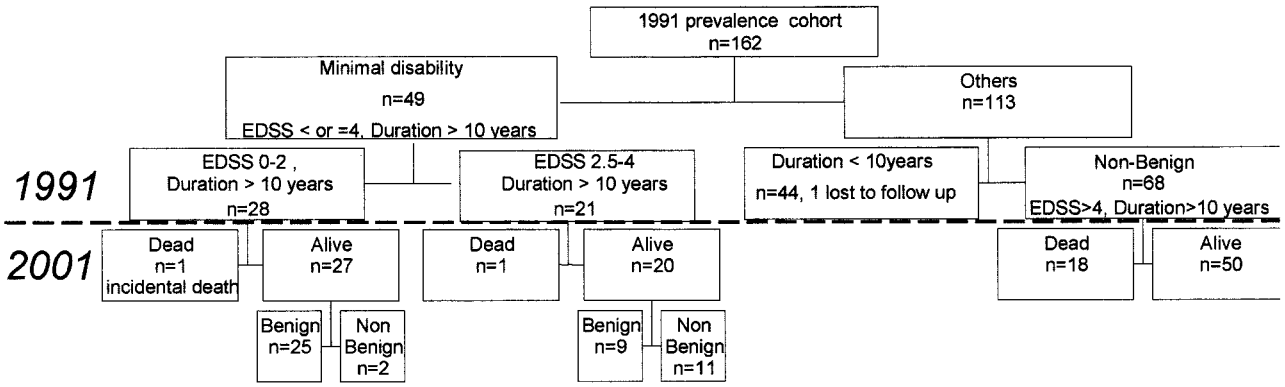

Fig 1. Patient profile of original 1991 Olmsted County multiple sclerosis prevalence cohort. 1991 data are shown above and 2001 data below the broken line. Benign in 2001 is defined as having Expanded Disability Status Scale (EDSS) score of 4 or lower and longer than 20 years. Nonbenign is defined as having an EDSS score higher than 4 duration of ms for longer than 20 years.

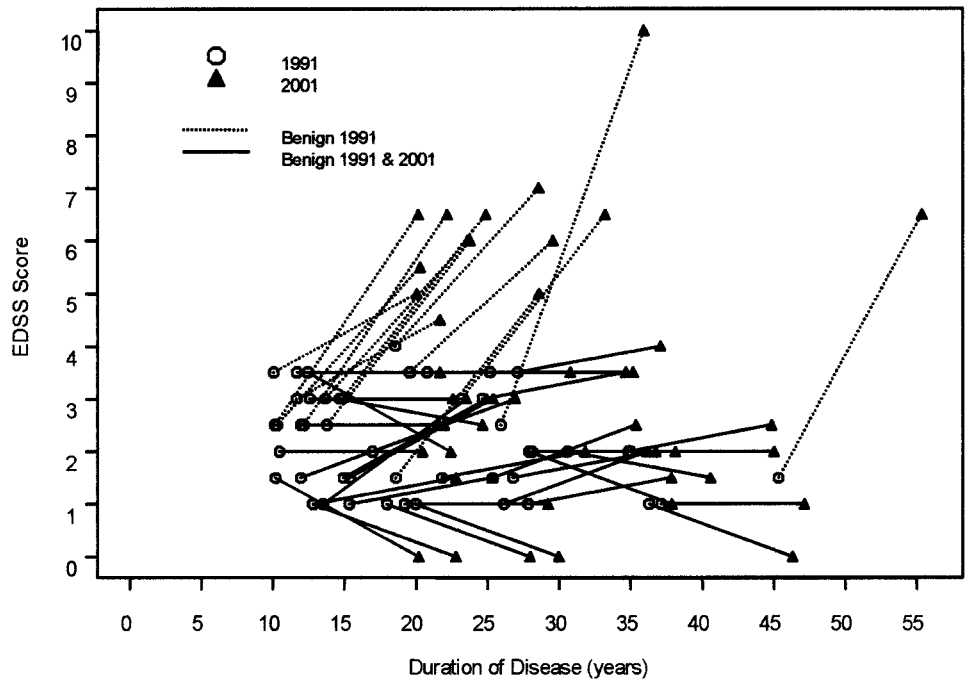

Fig 2. Change in Expanded Disability Status Scale (EDSS) over 10 years versus duration of disease in 1991. Each line represents an individual patient.

than 5 years were much less likely than those with EDSS 2.5 to 4 for a similar disease duration to progress to EDSS score higher than 4 or need a cane 10 years later ($p < 0.001$).

For Patients with Minimal Disability for More than 10 Years in 1991, How Were They Doing 10 Years Later?

Twenty-eight patients had EDSS score of 2 or lower and disease duration of at least 10 years in 1991 and all had RRMS. None were lost to follow-up. The mean duration of MS in 2001 was 30 ± 9.5 years. The mean 1991 EDSS was 1.4 ± 0.4 and increased to 1.9 ± 1.4 in 2001. Eighteen had EDSS score of 2 or lower and 25 had EDSS score of 3 or lower in 2001. One patient who died from cancer (EDSS score of 2 within 6 months of death) was excluded. Two patients with EDSS score of 1.5 in 1991 had further relapses with permanent disability (EDSS score of 5.0 and 6.0) in 2001. None developed SPMS. Most were employed (19) or retired (6) with only 2 unemployed. All described their QOL as satisfactory or better (mean, 8.5 ± 1.3). Therefore, patients with EDSS score of 2 or lower and disease duration of at least 10 years have

Table. Ten-Year Outcome by Baseline EDSS and Disease Duration

Baseline EDSS (in 1991)	Duration of MS at Baseline (from onset in years)	N	No. (%) Reaching EDSS >4 (in 2001)	No. (%) Reaching EDSS ≥6 (in 2001)
0–2	0–4.9	14	4 (29)	4 (29)
	5–9.9	12	0	0
	10–19.9	14	1 (7)	0
	20+	13	1 (8)	1 (8)
2.5–4	0–4.9	4	1 (25)	1 (25)
	5–9.9	6	3 (50)	2 (33)
	10–19.9	15	9 (60)	6 (40)
	20+	6	3 (50)	2 (33)

EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

a 93% chance of continuing to have low disability an additional decade later.

For Patients with Moderate Disability for Longer Than 10 Years in 1991, How Were They Doing 10 Years Later?

Twenty-one had EDSS 2.5 to 4 for at least 10 years in 1991 and all had RRMS. The mean duration of MS in 2001 was 26 years ± 7 years. The mean EDSS in 1991 was 2.8 ± 0.5 and increased to 4.8 ± 1.7 in 2001. Fourteen (67%) had a worsened score, 12 (57%) progressed to EDSS score of greater than 4 and 8 (38%) required unilateral or bilateral assistance to walk or worse (EDSS ≥6.0) and developed SPMS. One patient died of a gastrointestinal bleed in 1997 and EDSS recorded 6 months before death was 6.5.

Of the 20 patients still alive in 2001, most were employed (9 outside the home), 8 retired (6 early on disability), and 1 was unemployed. Seven had mixed feelings or were dissatisfied with their QOL (mean, 6.1 ± 1.9). Therefore, patients with EDSS 2.5 to 4 for at least 10 years have a 43% chance of continuing to have low disability an additional decade later.

Factors Associated with Having an EDSS Score of 4 or Lower after Disease Duration of at Least 20 Years

The frequency of different patient characteristic variables for patients with EDSS score 4 or lower and disease duration greater than 20 years were compared with those with EDSS greater than 4 and similar disease duration. Those with a motor pathway deficit at onset were significantly less likely to be in the mild group after 20 years (odds ratio, 0.27; 95% confidence interval [CI], 0.09–0.85; $p = 0.02$). No other differences between groups were identified.

A multiple logistic model showed that patients with a motor pathway deficit at onset (odds ratio, = 0.25; 95% CI, 0.08–0.78; $p = 0.02$) and longer duration of MS in 1991 (odds ratio, 0.75 for each 5-year increment; 95% CI, 0.60–0.96; $p = 0.02$) were significantly less likely to be in the favorable prognostic group.

Discussion

Our study demonstrates that the longer the duration of MS and the lower the disability, the more a patient is likely to remain stable and not progress. This is particularly powerful for patients with benign MS for 10 years or longer, although there is predictive value for the period beyond the first 5 years' duration. However, it is not possible to predict outcome with reasonable certainty within the first 5 years from onset.

Only 7% of patients with minimal or no disability (EDSS ≤2 and duration of disease of at least 10 years) attained an EDSS score of greater than 4.0 and none required a wheelchair after at least 20 years of follow-up. Note that this group of patients comprises 17% of the entire 1991 prevalence cohort. In contrast, 12 of 21 patients with EDSS score of 2.5 to 4.0 and disease duration of at least 10 years reached EDSS score greater than 4.0 after at least 20 years of follow-up. This group comprises 13% of the 1991 cohort.

We propose that benign MS be defined as patients with MS for 10 years or more who have EDSS score of 2 or less because they have less than 10% likelihood of developing significant disability.

These findings have implications for the shared decision-making process between patient and physician. For RRMS patients who present with a clinical history and a documented examination suggestive of an initial attack of MS at least 5 years previously, and at the time of the present examination have an EDSS score of 2 or less, this study indicates that they have a high likelihood (>90%) of continuing to have a low level of disability and a good quality of life for the next 10 years or more. This may have an impact on the decision to initiate immunomodulatory medications, should magnetic resonance imaging suggest lack of disease activity. This has major implications as this group

of patients accounts for nearly one in five of all MS patients.

Our findings are in agreement with other studies including a 10-year follow-up study of benign MS patients in Ireland and a US army study that found the best predictor of later course (next 10 years) was the 5-year disability status scale (DSS).[9,16,17] Others have described factors associated with a benign or adverse course.[5,9,18] Our study suggests that it is clinically not possible in the early course of disease, using variables analyzed in this study to determine which patients will be benign.

A strength of this study is that it is population based with full ascertainment. There are limitations. The EDSS is heavily weighted toward physical disability. Although we did not perform detailed neuropsychometric analyses, 23 of 25 patients (with EDSS score ≤ 2 for >10 years) that continued to do well an additional 10 years later had a normal Mini-Mental State Examination score.

These natural history data may assist physicians in conjunction with other clinical and radiological findings to better counsel patients in the shared therapeutic decision-making process.

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