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Clinical course in multiple sclerosis patients presenting with a history of progressive disease

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Abstract
Objectives: Determine the likelihood of worsening clinical status in the near-term course of progressive MS and evaluate the predictive validity of our diagnostic impression of progressive forms of MS.
Methods: Retrospective review of charts from 175 patients seen between 2000 and 2007 who were diagnosed with either primary or secondary progressive multiple sclerosis. Data extracted included demographic factors, neurological examination findings to determine EDSS, timed 25 foot walk (T25FW) when available, duration of symptoms, clinical course as documented on initial visit, and history of disease-modifying agent (DMA) use. Significant change in EDSS was defined as a change of one point or more from initial to final clinical evaluation. Significant change in T25FW was defined as a $\pm$20% difference from baseline.
Results: Of the 175 charts reviewed, 35 patients met criteria and had sufficient documentation to allow for EDSS abstraction. Twenty-four patients (68.6%) showed no significant change in EDSS from baseline while eleven patients (31.4%) worsened and none improved. For those patients that had T25FW data available, 6 out of 20 (30%) patients worsened while 11 (55%) showed no change. Three patients (15%) improved.
Conclusion: In this observational study at a tertiary care MS center, patients classified as progressive MS did not progress as often, or as rapidly, as previous studies have suggested. Greater than two-thirds of patients in this cohort, did not increase 1 step on the EDSS.

1. Introduction

In the absence of reliable radiological or biological markers, clinical phenotypes of multiple sclerosis were defined in the 1990's by their clinical course. Distinct from the Relapsing Remitting form of the disease, Primary progressive MS (PPMS)

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was defined as "disease progression from onset with occasional plateaus and temporary minor improvements," and Secondary Progressive MS (SPMS) was defined as an "initial RRMS disease course followed by progression with or without occasional relapses, minor remissions, and plateaus"(Lublin and Reingold 1996). These definitions implied that the accumulation of disability in PPMS and SPMS can be variable in rate, but is inherently continuous. Natural history studies have further asserted that once progressive, MS is characterized by a steady and inexorable neurological decline, and that the course of PPMS and SPMS become indistinguishable (Tremlett et al., 2005; Confavreux et al., 2000). However, such studies have also demonstrated that actual rates of disability accrual vary considerably, characterizing the dilemma of predicting clinical outcome in the individual patient, especially in shorter time intervals (Tremlett et al., 2005; Confavreux and Vukusic, 2008).

Progressive clinical courses in patients with multiple sclerosis (MS) are the most therapeutically challenging forms of the disease primarily because of the lack of convincing clinical trial data and several recent negative studies (Wolinsky et al., 2007; Montalban, 2004; Leary et al., 2003; Hawker et al., 2009). Attempts to assess the efficacy of immunomodulatory agents such as glatiramer acetate in progressive patients have been hampered by rates of progression being neither as continuous nor as rapid as predicted (Wolinsky, 2004). This has resulted in inadequate numbers of subjects in clinical trials meeting disability outcomes to demonstrate a therapeutic effect.

Entrance criteria for clinical trials of PPMS and SPMS begin with the assumptions of continuous progression implicit in the definitions of these subtypes. At our tertiary care center, observations of patients felt to have progressive forms of MS have suggested protracted periods of clinical stability without clinical worsening. In this study we sought to determine the likelihood of worsening clinical status in the near-term course of progressive MS. To evaluate the predictive validity of our diagnostic impression of progressive forms of MS, we evaluated the rates of disability accrual in patients classified to have progressive MS at the time of their initial presentation to our MS Center.

2. Methods

After obtaining approval from Mount Sinai Medical Center's institutional review board (IRB), we reviewed charts of patients seen between 2000 and 2007 who were diagnosed with either primary or secondary progressive multiple sclerosis.

Patients included in the study were those who met diagnostic criteria for multiple sclerosis based on their clinical history, neurologic exam and supporting paraclinical data (Polman et al., 2005). They were further classified into established PPMS or SPMS subtypes based on the patient's clinical history of ongoing progression (Lublin and Reingold, 1996). At least two documented visits at a minimum of 1 year apart were also required, with available data to allow for Expanded Disability Status Score (EDSS) determination. Exclusion criteria were defined as a history of relapses at any point after onset of progression, insufficient clinical data to extract EDSS, and major superimposed non-MS related causes of neurological disease (stroke, neuropathy, etc.).

Data extracted included demographic factors, neurological examination findings and self-reported walking distance to determine EDSS, timed 25 foot walk (T25FW) when available, duration of symptoms, clinical course as documented on initial visit, and history of disease-modifying agent (DMA) use. Significant change in EDSS was defined as a change of one point or more from initial to final clinical evaluation (Goodkin, 1991). Significant change in T25FW was defined as a $\pm$20% difference from baseline (Schwid et al., 2002; Kragt et al., 2006).

2.1. Statistical analysis

Continuous variables are reported with medians and ranges. Frequency tables were used to categorize patients as either worse, improved or no change for both clinical measures. To analyze patterns of progression, the group was divided into two subsets to see whether patients with an EDSS $</=4$ were less likely to show progression than those patients with an EDSS >4, utilizing a Pearson Chi-Square test (Confavreux and Vukusic, 2008; Hobart et al., 2000). All statistical analyses were performed by using the Statistical Package for Social Sciences version 16.0. (SPSS, Inc., Chicago, IL, USA).

3. Results

Of the 175 charts reviewed, 35 patients met inclusion criteria and had sufficient documentation to allow for EDSS abstraction. Of the patients that did not meet criteria, a majority of them were excluded due to insufficient clinical data to extract EDSS. Complete demographic and baseline data are summarized in Table 1. Baseline EDSS scores at entry ranged from 2.0 to 9.5 with a median EDSS score at baseline of 5.5. Mean age at onset of progressive symptoms was 47.1 years. Mean duration of follow up was 43 months (range 17–96 months). The mean number of visits during follow-up (including the initial visit) was 4.5 (range of 2–8 visits).

Of the 35 patients included, twenty-four patients (68.6%) showed no significant change in EDSS from baseline while eleven patients (31.4%) worsened by at least 1 step and none improved. Of the eleven patients that worsened, six (54.5%) had an EDSS score $\leq$4, and five (45.5%) had an EDSS >4 at the time of their initial visit ($p=0.41$). Of the twenty-four patients that were stable, 18 (75%) were on a disease-modifying agent ($p=0.65$). Based on Chi-square analysis, none of these dichotomous variables significantly predicted ongoing progression. Mean disease duration for

Table 1 Distribution of clinical measures at baseline and final visits.

Outcome measure	Mean	Median	Standard deviation	Number
EDSS at baseline	5.36	6.0	2.24	35
EDSS at last visit	6.14	6.5	2.16	35
T25FW at baseline	10.32	8.0	5.35	21
T25FW at last visit	13.81	8.54	12.89	21