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Relapsing multiple sclerosis patients treated with disease modifying therapy exhibit highly variable disease progression: A predictive model

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ABSTRACT

Objective: To describe a "new natural history" of multiple sclerosis (MS), characterizing three patterns of progression in Relapsing MS (RMS) patients during the "treatment era," using newly developed definitions. By utilizing our simple model we intend to predict which patients are most likely to reach an EDSS of 6.0.
Methods: We stratified MS progression into three distinct patterns: aggressive MS (AMS), intermediate MS (IMS) and mild MS (MMS), based on Expanded Disability Status Scale (EDSS) score rate of change. These groups were compared for progression of EDSS before and after reaching these definitions.
Results: The three groups remained significantly different in terms of disability throughout their disease courses $p \leq 0.001$; 98% of the patients used disease modifying treatments (DMTs). AMS patients represent a significantly more disabling and aggressive form of MS than the IMS group.
Conclusions: Transition from relatively mild MS to aggressive course may begin at any time in the first 15 years, despite DMTs. Our definition for AMS is unique and identifies a group of patients who become permanently disabled within two years after a variable amount of time in a benign phase, despite treatment with modern DMTs.

1. Introduction

The definition of secondary progressive multiple sclerosis (SPMS) has always been imprecise and subjective, even using the most accepted recommendations for determining the onset of this critical phase of relapse onset multiple sclerosis (RMS) [1]. A systematic scoring system has never been used to identify or to characterize onset of the progressive phase of RMS [2]. Most patients with disabling features of multiple sclerosis (MS) are considered to be "secondary progressive," after a relapsing onset, with primary progressive disease (insidious onset of symptoms and disability) considered less common. Rare attempts to identify and to characterize the most rapidly disabling forms of MS using more specific definitions are sparse and largely limited to early multiple sclerosis [3]. More specific descriptions of patterns of progression, if applicable to large numbers of patients, might provide new opportunities for understanding progressive disease. Models using definitions describing more severe patterns of MS may be useful

Abbreviations: ALS, amyotrophic lateral sclerosis; AMS, aggressive multiple sclerosis; AMSTC, allegheny multiple sclerosis treatment center; CI, conference interval; DMTs, disease modifying treatments; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; HR, hazard ratio; INF, interferon beta; IMS, intermediate multiple sclerosis; MS, multiple sclerosis; MMS, mild multiple sclerosis; OR, odds ratio; η_p^2, partial eta squared; RMS, relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

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to clinicians who treat MS, allowing improved risk/benefit analysis when considering the array of treatment options now available. Identification of a severe course of MS early in the disease, which is predictive of continued worsening, would be particularly useful. Stratification of patients according to risk of disease progression is especially important when considering "treatment escalation" strategies which are expected to emerge as newer highly efficacious, albeit potentially toxic agents are becoming available [4]. A more precise classification of patients based on disease behavior may also be useful in the design of clinical trials.

In our experience in the clinic, after many years of showing a benign pattern, some RMS patients transition relatively rapidly to more a severe decline, with this transition becoming apparent over one or two years. We sought a definition for this picture of aggressive MS (AMS), and recently applied this definition to a long-term data set from a clinical trial [5]. As a logical contrast we were also able to create mutually exclusive definitions for two other groups of patients according to the disease course, a mild MS group (MMS) and a group with intermediate severity (IMS). We found that the AMS group remained more disabled over time compared to the IMS, but we were unable to show that the AMS group continued to show a more rapidly progressive course relative to the IMS group. We now expand our exploration using a new group of patients who were continually followed since diagnosis, to document the pattern of aggressive MS versus less aggressive phenotypes of relapsing multiple sclerosis seen in the first 15 years of RMS. Our unique data set includes a group of over 200 patients followed at our center during the "treatment era of MS," providing new natural history data in the modern era. We also explore whether the risk of development of AMS decreases over time during the first 15 years after onset.

2. Materials and methods

2.1. Standard protocol approvals

Data were collected from our clinic patient records after approval by the Institutional Review Board and Ethics Board at Allegheny General Hospital (Pittsburgh, PA).

2.2. Participants

The records of all patients who attended the Allegheny MS Treatment Center (AMSTC) at Allegheny General Hospital in Pittsburgh, Pennsylvania from 1989 to 2006 and met the McDonald criteria for a diagnosis of MS were screened for inclusion in this study [6]. Patients were included if they were evaluated within 12 months of a second disease defining attack or had serial MRI changes, leading to a diagnosis of MS. Patients were excluded if they had: (1) less than two years of MS symptoms from onset until final follow up, as we were focused on the development of sustained progression measured over two or more years; (2) fewer than two examinations by the lead investigator (TS), at least six months apart at the AMSTC; (3) progressive onset of disease, as previously defined [1], leading to a diagnosis of primary progressive MS; and (4) a description of two or more possible attacks of demyelinating disease occurring more than one year prior to presentation to our clinic (i.e., these patients were or could have been diagnosed more than one year prior to presentation to our clinic).

2.3. Records reviewed and data collected

Records were reviewed for patients initially seen between February 1989 and December 2006, with follow-up information obtained for visits through November 2012. Data collected included: demographics (age, gender and ethnicity), date of MS onset, date of second attack of MS, date of first visit, dates of Expanded Disability Status Scale [7] (EDSS) evaluations and EDSS scores, dates and type of initial disease modifying treatment (DMT); interferon beta (Avonex, biogen idec, Weston, MA) or glatiramer acetate (Copaxone, Teva Pharmaceutical Industries Ltd., North Wales, PA) and initial date of natalizumab (Tysabri, biogen idec, Weston, MA) therapy. Records were reviewed for accuracy of diagnosis and confounding comorbidity.

2.4. Defining aggressive, intermediate and mild multiple sclerosis

Patients who met inclusion criteria were categorized into one of three groups, based on disease progression. Patients reaching, at any point, an EDSS of 4.0 (sustained for at least six months) or more by advancing two or more EDSS points within two years were termed "aggressive MS" (AMS, group 1). Although this definition is modest [3,8] compared to prior studies of severe MS, a previous study suggested patients meeting these criteria do poorly as a group and we wished to verify the predictability of this model in a separate data set [5]. Patients attaining EDSS 4.0 (sustained for at least six months) less rapidly, not by progressing two or more EDSS points within two years, were categorized as "intermediate MS" (IMS, group 2, mutually exclusive from AMS). Finally, patients who did not reach a sustained EDSS 4.0 at any point in their disease state were termed "mild MS" (MMS, group 3).

2.5. Five-year epochs

As a means of examining a possible change in the risk of development of AMS over time, the AMS group was stratified into five-year epochs (0–5, 6–10, 11–15 and >15 years from onset) based on the disease duration when MS became aggressive by our definition.

2.6. Statistical analysis

Statistical analyses were performed using the SPSS v 20.0 software (SPSS Inc., Chicago, IL).

2.7. Comparison of three groups (MMS, IMS and AMS) and overall disease course

Summary statistics for all three groups (MMS, IMS and AMS) were calculated for gender, age, disease duration, follow-up time, EDSS at MS diagnosis, sustained EDSS after second attack and sustained EDSS at last exam. Additional summary statistics included: percent of patients treated with a DMT, type of first DMT, disease duration from diagnosis and symptom onset to date of first MS medication. We also examined the percent of patients treated with natalizumab and disease duration at first dosage of natalizumab. We used a 3×15 lower bound mixed design ANOVA with bonferroni post hoc correction to test for group effects (MMS, IMS and AMS) on time and disability (EDSS) during the first 15 years of MS. We measured the effect size of the model by using partial eta squared. Additionally, we used Kaplan–Meier survival analyses to depict time to several disability outcomes (AMS, EDSS 3.0, 4.0 and 6.0) and we tested sensitivity, specificity, positive predictive value and negative predictive value of patients reaching EDSS 6.0. These EDSS milestones (3.0, 4.0 and 6.0) have been chosen by previous natural history studies, were deemed important in terms of predictability and can be "easily determined retrospectively" [9,10].

2.8. Comparison of IMS and AMS

We utilized Kaplan–Meier survival analyses (log rank) to calculate the disease duration and age when patients reached EDSS 4.0. A forward stepwise Cox regression analysis was used to examine factors associated with time to reach EDSS 4.0 and we examined