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Relationship between symptom change, relapse activity and disability progression in multiple sclerosis

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ABSTRACT

Background: Symptom changes may serve as a risk factor for relapse activity (RA) and disability progression (DP), which could facilitate multiple sclerosis (MS) treatment decisions.
Objective: To assess the relationship of symptom change with RA and DP.
Methods: We evaluated the relationship of symptom change with subsequent RA and DP using NARCOMS registry data reported over a five-year period. Symptom change was evaluated using both symptom worsening (SW) and average of Performance Scales (APS) scores. Disability progression was defined as a one-point or more increase in Patient-Determined Disease Steps (PDDS) score between two consecutive updates. Repeated measures logistic regression was used to investigate the relationship between symptom change and RA and DP.
Results: SW and APS were both significant predictors of subsequent RA and DP. Both SW and APS have a significant interaction with levels of disability (Mildly Impaired versus Highly Impaired) for the prediction of the subsequent RA or DP. For Mildly Impaired MS subjects, both SW and APS were significant predictors of both RA and DP. However, for Highly Impaired MS subjects, SW did not significantly predict future RA and neither SW nor APS predicted disability progression.
Conclusion: Changes in self-reported overall symptomatology may precede and predict clinical relapse and future disability progression. The predictive power of symptom changes may only be present at lower levels of disability.

1. Introduction

Multiple Sclerosis (MS) is an inflammatory, immune-mediated disease that targets the central nervous system (CNS) [1–3]. MS affects approximately 400,000 individuals in the United States [4–7]. Approximately 85% of these individuals have relapsing forms of MS (RRMS), where worsening most commonly occurs by relapse and incomplete recovery from acute relapses [8]. In progressive forms of MS, worsening most commonly occurs by gradual progression of neurological disability in the absence of acute relapses [9,10]. Even during remissions in RRMS, MRI studies show that CNS inflammatory activity may persist in the absence of acute symptom relapses [11]. If left untreated, within 25 years approximately 90% of persons with RRMS will enter the secondary progressive phase of MS (SPMS) [12–17]. In SPMS, disability progression is more resistant to treatment than in RRMS [2,9,14,17–20]. Therefore, preventing or delaying the accumulation of irreversible disability and the transition to SPMS are central goals of the disease management in patients with RRMS.

Relapse activity is often considered an indication of breakthrough disease and suboptimal response to disease-modifying therapy (DMT) in MS. Ongoing CNS inflammation involves both axonal damage and reparative processes. As more and more irreversible neurological damage occurs during the CNS inflammation, relapses eventually lead to accumulation of disability and disability progression (DP). Symptom change, with or without an acute relapse, could be a more subtle clinical manifestation of these inflammatory processes. Therefore, we hypothesized that symptom changes may be related to ongoing inflammation and serve as a risk factor for more overt clinical relapse activity and disability progression. A better understanding of the nature of such associations may provide useful information for disease management and treatment

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decisions. We evaluated this hypothesis by utilizing NARCOMS, a large, longitudinal MS patient registry where overall symptoms change and clinical relapses are reported every six months.

2. Methods and materials

2.1. Cohort disposition

This was a retrospective cohort study using data from the North American Research Committee on Multiple Sclerosis (NARCOMS) self-report registry from 2006 through 2010. Participants in this analysis reported having relapsing disease course in 2006 and completed two updates in each of the next five years yielding a total of 10 semi-annual updates per participant. Excluding those with missing surveys and using only those with complete data provided an equal space epoch of time for consistency and minimization of recall bias due to extended time between follow-up surveys. To assess the generalizability of the participants included in the analysis, we compared the demographics of these participants to those with less frequent survey responses; the two subsets of participants did not significantly differ on any sociodemographic characteristics.

2.2. Primary outcomes

The primary outcomes of the analyses were relapse activity and disability progression. Relapse activity was treated as a dichotomous variable based on participants' responses to a survey question as to whether or not the participant had a relapse in the past 6 months. NARCOMS defines a relapse as a "development of new symptoms or worsening of old symptoms that lasts longer than 48 h" that occurs at least 30 days after a previous relapse. In this study, all participants were given this definition at each survey prior to the questions being presented on the form. Disability status is reported using the Patient Determined Disease Steps (PDDS) [21]. PDDS is a validated nine-point self-report instrument (ranging from 0 = normal to 8 = bedridden) which has been shown to correlate strongly with the Expanded Disability Status Scale [22]. Overall disability progression (DP) was defined as at least a one-point increase in PDDS score between two consecutive updates.

2.3. Symptom change

Symptom change was evaluated using both symptom worsening and the Performance Scales scores. At each semi-annual survey, subjects were asked "Over the last 6 months, have your MS symptoms worsened in a gradual, progressive manner (not due to relapses or exacerbations)?" The responses to this question (Yes, No) were used as a measure of symptom worsening (SW).

Performance Scales (PS©)[1] were used to assess specific symptoms in participants [23,24]. The PS are a single question for each of eight domains: mobility, bowel/bladder, fatigue, sensory, vision, cognition, spasticity, and hand function. All of the subscales are scored using a six-point scale (0 = normal, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, or 5 = total disability), except the mobility subscale which includes a seventh response category (0 = normal, 1 = minimal gait, 2 = mild gait, 3 = occasional use of cane or unilateral support, 4 = frequent cane use, or 5 = severe gait, bilateral support, 6 = total gait disability or bedridden). An average Performance Scales score (APS) was determined for each update survey by taking the sum of the subscale scores (bowel/bladder, fatigue, sensory, vision, cognition, spasticity, and hand function) and dividing it by the number of PS subscales the participant completed. Mobility was not included in the APS as it was found to be highly correlated with PDDS (Spearman correlation coefficient = 0.96; $p < 0.001$). To ensure that APS scores were representative of the overall symptom severity of patients, participants had to have completed at least five out of seven Performance Scales (PS); 61 participants (0.2%) were excluded from the analysis due to incomplete PS data.

The start of the assessment period in 2006 is considered the baseline for socio-demographic covariates considered: age, gender, race, education, employment, insurance and household income level; and disease status including: PDDS and disease modifying treatment (DMT) status. Disease history is measured from NARCOMS enrollment information to 2006 including: age at symptom onset, year of symptom onset, year of diagnosis, disease duration, and relapse history.

2.4. Statistical analysis

These data permitted multiple intervals of assessment per participant and thus we used generalized estimating equations (GEE) to handle the dependence between the repeated measures. We used logistic regression models to evaluate the relationship between symptom progression and relapse activity in the subsequent 6 months and 12 months. Logistic regression models were also used to investigate the effect of symptom progression on disability progression in the subsequent 6 months. Additional covariates were chosen for the model using a forward selection procedure; in order to be included in the final model, covariates had to either be statistically significant at the $\alpha = 0.05$ level or change the estimate of the effect for SW by more than 10%. We then repeated this model selection and fitting using disability progression as the response variable, instead of relapse activity.

3. Results

3.1. Cohort characteristics

A total of 2605 participants with relapsing disease completed ten consecutive update surveys from 2006 to 2010. Of those, 1687 (65%) participants had PDDS levels ≤ 4 at baseline, considered to indicate mild impairment, or less severe, relapsing MS (Mildly Impaired MS cohort). We designated the 918 (35%) participants with more severe relapsing MS (i.e., PDDS levels > 4 at baseline) as the Highly Impaired MS cohort. The participant socio-demographics and clinical characteristics at baseline are presented in Tables 1 and 2, respectively. The Mildly Impaired and Highly Impaired MS cohorts significantly differed in age, disease and symptom duration, gender ratio, education level, and use of disease-modifying treatment. The two cohorts did not significantly differ at baseline in rates of relapse activity or symptom worsening in the prior 6 months ($p > 0.10$ from a chi-square test for both). Overall, 1182 (45.4%) participants reported SW in the 6 months prior to the baseline 2006 survey. To obtain a more nuanced picture of symptom worsening, participants were asked the follow-up question "Compare your overall MS symptoms now with what you experienced 6 months ago (much worse, worse, a little worse, no change, a little better, better, or much better)". Of the 1182 participants reporting symptom worsening, 58 (4.9%) reported that their symptoms were "much worse" than 6 months ago, 298 (25.2%) reported "worse" symptoms, and 760 (64.3%) responded that their symptoms were "a little worse" than 6 months prior; for the remaining 66 participants, despite having reported that their MS symptoms had worsened in the previous 6 months, responded to this question with "no change", "a little better" or "better".

Overall, 934 (35.9%) participants reported a relapse in that same time period. Between Spring 2006 and Fall 2010, amongst those reporting SW in the preceding 6 months, the proportion that reported at least one relapse over the following 6 months decreased from 41.3% in the first survey interval to 23.4% over the successive 6 month intervals during this 5 year period of observation. Similarly, reported

[1] While there are multiple performance scales, we use here only the eight subscales described above. Copyright information for these scales is as follows: Performance Scales, Copyright Registration Number/Date: TXu000743629/1996–04-04; assigned to DeltaQuest Foundation, Inc., effective October 1, 2005. U.S. Copyright law governs terms of use.