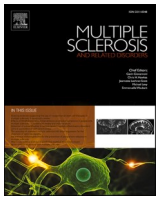
Multiple Sclerosis and Related Disorders 46 (2020) 102585

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original Article

A longitudinal study of symptom botheration in Multiple Sclerosis.

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ARTICLE INFO

Keywords:
Multiple sclerosis
Symptoms
Longitudinal study
Disability
Fatigue

ABSTRACT

Background: It is well documented that ambulatory disability in MS worsens over time, but there is a dearth of information on symptom evolution in other domains commonly affected by MS.
Methods: SymptoMScreen (SyMS) is a validated tool for assessing symptom severity in 12 domains commonly affected by MS. Patients who attended two specialized MS centers filled out SyMS at each visit. We included in the study patients with neurologist-diagnosed MS who completed two SyMS questionnaires separated at least 12 months. We used the first and final assessment and adjusted for time on study, baseline SyMS score, age, sex, race, MS type, disability strata, and site. Changes over time were also examined using Markov chain estimates of moving from one level of botheration to another for each domain over 1-year periods.
Results: A total of 1,014 MS patients met the inclusion criteria. Mean composite SyMS score was 1.4 (±1.16) at baseline and increased by 0.084 (±0.73) points during 21.0 (±5.5) months of followup ($p<0.0001$). The initial mean composite SyMS score correlated strongly with the final mean composite SyMS score ($r=0.81$). Individual domain SyMS scores at baseline were highest for fatigue: 2.2 (±1.7), and lowest for vision: 1.1 (±1.3) and dexterity: 1.1 (±1.4). Small but significant increases during followup were seen in dexterity, bladder, vision, and pain domains, while significant decreases were seen in anxiety and sensory domains. We observed a high degree of inter-individual variability in symptom severity with the more extreme scores tending to resolve over time.
Conclusions: Symptom botheration increases modestly year-to-year, as would be expected in a slowly progressive disease that evolves over decades. Initial symptom burden strongly correlated with final symptom burden, but there was a high degree of individual variability in symptom severity.

1. Introduction

The pathologic hallmarks of multiple sclerosis (MS) are diffuse, immune-mediated neurodegeneration and accrual of focal demyelinating lesions throughout the central nervous system. Consequently, patients with MS typically experience symptoms in multiple neurologic domains. Weakness, fatigue, urinary frequency, depression and pain are highly prevalent in MS (de Sa et al., 2011, Nagaraj et al., 2013, Nazari et al., 2020, Bakshi, 2003, Fitzgerald et al., 2018). Cross-sectional studies demonstrate that overall symptom burden and the physical component score of health-related quality of life are higher in those with longer disease duration (Kister et al., 2013, Wu et al., 2007). Yet, there are few longitudinal studies that examined how symptom severity in MS patients evolves across multiple domains (Liu et al., 2016, Bruce and Arnett, 2008, Schreurs et al., 2002).

The objective of the present study was to document changes in symptom severity in multiple neurologic domains commonly affected by MS in an ethnically diverse cohort followed over a period of 1-4 years in two specialized MS centers. The symptoms were assessed using symptoMScreen (SyMShttps://www.symptomscreen.org/), a battery of 7-point Likert scales for 12 distinct domains: mobility, dexterity, spasticity, bodily pain, sensation, bladder function, fatigue, vision, dizziness, cognition, depression, and anxiety (Green et al., 2017). SyMS has been shown to have excellent reliability, criterion validity, construct convergent and divergent validity in MS patients in several cohorts (Green et al., 2017, Fitzgerald et al., 2019, Meca-Lallana et al., 2020, Kister et al., 2019). SyMS defines symptom severity in relation to the impact on patients' daily functioning and is therefore easily interpretable (Khurana et al., 2017). SyMS is freely available to clinicians and researchers (www.symptomscreen.org) and takes less than 2 minutes to complete, making it an attractive choice for assessing patient-reported outcomes (PRO) in a busy clinical practice.

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https://doi.org/10.1016/j.msard.2020.102585
Received 1 July 2020; Received in revised form 14 October 2020; Accepted 15 October 2020
Available online 17 October 2020

2. Methods

Consecutive patients from the urban New York University (NYU) MS Care Center (New York City, NY) and the suburban Barnabas MS Care Center (Livingston, NJ) filled out SyMS before the start of a doctor visit as part their routine clinical care. Patients self-assessed their disability with Patient-determined Disability steps (PDDS), an eight-point scale that measures global neurological impairment in MS (Hohol et al., 1995) and correlates strongly with the Expanded Disability Status Scale (EDSS) (Learmonth et al., 2013). At each visit, the clinician confirmed the diagnosis of MS (2010 McDonald's criteria) (Polman et al., 2011) and documented disease subtype.

We included in our study all patients who had two SyMS filled out at least 12 months apart. The 'dizziness' domain was introduced into SyMS during followup period and therefore could not be collected on about 20% of earlier responders. Out of 1,014 patients, 36 patients had one missing (non-dizziness) domain score at baseline and 110 patients had one missing score at followup. Six patients at baseline and 15 at followup were missing 2 domain scores; 4 patients at baseline and 7 at followup were missing 3 domain scores. Imputation was used for these individuals by calculating the average score for the items present and scaling these values to a 12-domain score. All visits took place between June 2010 and December 2018. The study received an exemption determination from the institutional review boards (IRBs) of NYU Langone Medical Center (New York) and Barnabas Medical Center (Livingston, NJ). In order to meet the IRB exempt review status, we excluded patients younger than 18 years old and those who could not follow written instructions in English.

Analyses included descriptive statistics, plots of mean scores over time and multiple regression analyses. We used the first and final assessment and adjusted for time on study to measure changes over time within the cohort adjusted for baseline SyMS Score, age, sex, race, MS type, PDDS < 3 and $>=3$ and site. Followup time was adjusted by computing the rate of change per year and using this as the outcome. Changes over time were also examined using change tables for 1-year periods, so-called Markov chain estimates of moving from one level of botheration to another for each domain. These estimates were obtained using conditional probabilities.

All analyses were carried out using JMP and SAS software; $p < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics and SyMS scores

A total of 1,014 consecutive MS patients from NYU (n = 576) and Barnabas (n = 438) MS Care Centers met our criteria and were included in the study. Demographic characteristics for the cohort are shown in Table 1.

Table 1
Demographic characteristics.

N	1014
% Female	74%
Age in years at first visit, average (SD)	44.7 (12.4)
Initial PDDS median, average (SD), range	1, 2.0 (2.0), [0-8]
Ambulatory assistance (PDDS >3) at first visit, %	31%
Initial Disease type, %	
Relapsing	87%
Progressive	13%
Race, %	
White	60.4%
AA	18.6%
HA	13.5%
Other	7.5%

Legend: SD – standard deviation; PDDS – Patient-determined Disability Steps; AA – African-American; HA – Hispanic-American.

At baseline, the mean composite SyMS (average across all domains) was 1.4 (±1.16) and the median was 1.1. Distributions of mean composite SyMS scores and self-rated disability scores (PDDS) at baseline are shown in Fig. 1. There was a high degree of correlation between mean composite SyMS score and PDDS (r^2=0.76), which demonstrates appropriate convergent validity of SyMS with the overall disability as assessed with PDDS. (These results are consistent with prior studies (Green et al., 2017, Fitzgerald et al., 2019, Meca-Lallana et al., 2020, Kister et al., 2019.)

Mean individual domain SyMS scores for each of the 12 domains are shown in Table 2. The highest domain score at baseline was fatigue: 2.2 (±1.7); the lowest were vision: 1.1 (±1.3) and dexterity: 1.1 (±1.4); walking score was intermediate: 1.8 (±1.8). The distribution of baseline domain SyMS scores are shown on a heatmap in Table 3. The domains with the highest proportion of patients with the three most severe grades were fatigue (25% of patients were in the three most severe grades), walking (19%), followed by spasticity, pain, sensory symptoms, bladder function, cognition (13-15% for each of these domains). The domains with the lowest proportion of patients in the three most severe grades were vision (6%) and dexterity (7%). For each of the domains, a third to almost half of all patients reported no botheration (score of 0).

3.2. Longitudinal followup

Mean duration of followup was 21.0 (±5.5) months (range: 12.0 - 38.1 months). During followup, the mean composite SyMS score increased by 0.084 (±0.73) points, p<0.0001 (95% CI 0.039 - 0.13). Mean composite SyMS score changed by more than 0.5 points in 22.2% of patients and by more than 1 point in 8.3% of patients. The initial mean composite SyMS score correlated highly with the final mean composite SyMS score (r=0.81). In the multivariable regression model that was adjusted for baseline SyMS score, age, sex, race, MS type, only higher baseline PDDS weakly predicted a worsening in SyMS score (p=0.047), but after adjusting for the followup time, the stratification was no longer significant (p=0.12). Changes for the individual SyMS domain scores are shown in Table 3. Small, but significant increases were observed in dexterity, bladder, vision, and pain domains, and decreases – in anxiety and sensory domains. All other domains showed non-significant increases, except for depression score, which decreased marginally.

The dynamics of symptoms changes for individual patients are depicted in the Sankey diagram in Fig. 2. The number of patients with a given maximum grade in any domain at baseline is shown on the left y-axis, and at the last followup - on the right y-axis; the widths of streamlines is proportional to the number of patients within each of the categories at baseline and follow up. For example, there were a total of 131 patients who had at least one domain score=5 (but no scores higher than 5) at baseline and a total of 139 patients who had at least one domain score=5 (but no higher scores) at followup. The diagram shows that the vast majority of patients with a maximum score=5 at the last followup are the patients who had maximum scores of 4 (purple streamline), 5 (red streamline) and 6 (blue streamline) at baseline.

To further quantitate symptom variability with time, we calculated probabilities that patient maximum domain scores progressed above a specified threshold during the first year of followup in any one domain, or regressed below this same threshold. These data are shown in Fig. 3. For example, a patient with domain scores=0 at baseline had a 52% probability of developing at least one score=1 or more over the first year period (0.52 isshown) above the forward arrow), while a patient with at least one domain score=1 or more had a 3% probability of having all domain scores revert to zero at the end of the first-year period (as indicated as 0.03 below the backward arrow). Conversely, for patients whose domains scores were all <6 at baseline, the probability of developing at least one domain score=6 was 4%, while the probability of regressing to all domain scores of <6 for a patient who had at least one score of 6 at baseline was 53%. The probability of progressing and

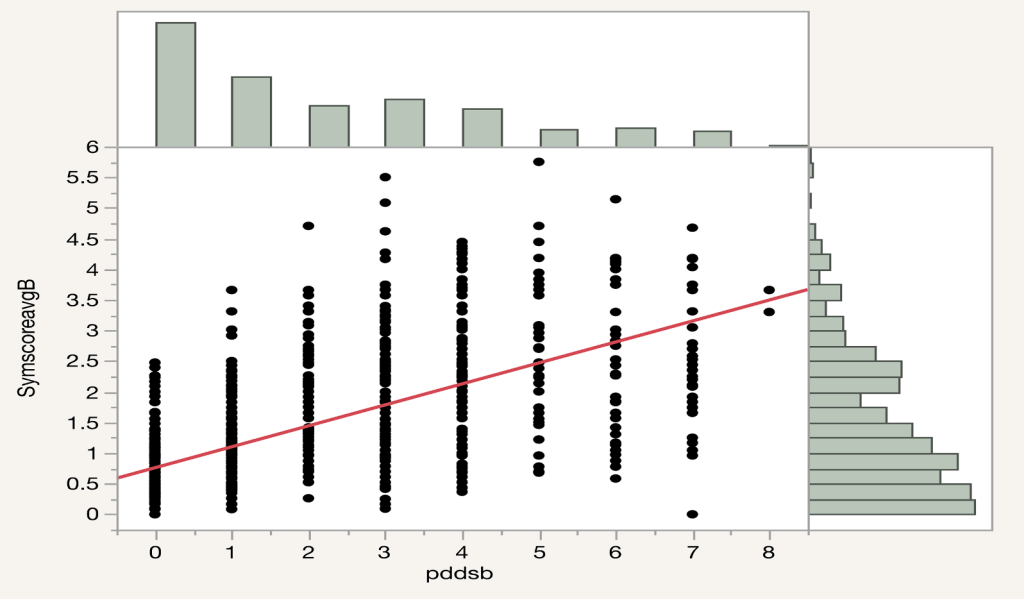

Fig. 1. Distribution of mean composite SyMS Scores and PDDS Scores at Baseline, and correlation between SyMS and PDDS.
Legend: Distribution of mean composite SymptoMScreen Scores at baseline is shown in a bar graph on top of x-axis, and of Patient-Determined Disability Scores – on the right of y-axis. SymptoMScreenavgB – mean composite SyMS score at baseline; PDDSb - Patient-Determined Disability Scores at baseline

Table 2
Distribution of SyMS Domain Scores at Baseline.

	walking	hand	spasticity	pain	sensory	bladder	fatigue	vision	dizzy	cognitive	depression	anxiety	
6	4%	1%	2%	3%	2%	3%	3%	1%	0%	1%	2%	2%	0%
5	5%	2%	4%	5%	4%	3%	8%	2%	4%	4%	4%	3%	10%
4	10%	4%	8%	8%	8%	7%	14%	3%	6%	8%	5%	5%	20%
3	14%	9%	14%	12%	14%	11%	18%	10%	11%	13%	12%	15%	30%
2	11%	14%	17%	13%	18%	18%	18%	14%	10%	17%	11%	14%	40%
1	24%	24%	20%	17%	25%	19%	21%	23%	21%	25%	21%	22%	50%
0	32%	46%	34%	43%	29%	39%	18%	47%	48%	32%	46%	39%	

Legend: Heatmap provides distribution of domain scores at baseline. Color coding of frequency (red – for least frequent, 0-10%, green – most frequent, 40-50%) is shown on the right.

Table 3
Baseline domain SyMS scores and change in domain scores during follow up.

Domain	N	Baseline domain SyMS, mean (SD)	Change during follow up (SE)	p
Walking	879	1.8 (1.8)	0.04 (0.039)	NS
Dexterity	**976**	**1.1 (1.4)**	**0.17 (0.037)**	0.0001
Spasticity	987	1.6 (1.6)	0.04 (0.039)	NS
Pain	**989**	**1.5 (1.7)**	**0.09 (0.038)**	**0.02**
Sensory	**997**	**1.7 (1.6)**	**-0.08 (0.039)**	**0.03**
Bladder/ bowel	**1000**	**1.5 (1.6)**	**0.14 (0.04)**	**0.0003**
Fatigue	990	2.2 (1.7)	0.02 (0.041)	NS
Vision	**997**	**1.1 (1.3)**	**0.09 (0.037)**	**0.02**
Dizziness	228	1.2 (1.5)	0.13 (0.091)	NS
Cognition	1001	1.6 (1.5)	0.01 (0.037)	NS
Depression	1006	1.3 (1.6)	-0.01 (0.037)	NS
Anxiety	**886**	**1.4 (1.5)**	**-0.1 (0.045)**	**0.03**

Legend: Domains with a significant change over followup period are shown in bold. N – number of responders at baseline. SD – standard deviation; SE – standard error; NS – non-significant (<0.05); SyMS – symptoMScreen.

regressing over each threshold during the second year of followup was very similar to the probabilities over the first year of follow up (data not shown).

We further investigated whether individuals who report changes in their disability score (PDDS) would have corresponding changes on their SyMS. In a multiple regression model, the rate of change of the PDDS and baseline SyMS were the only predictors of rate of change in SyMS, while age, sex, race, and disease type were not predictive of the rate of change in SyMS. Overall, there were no race effects, but Hispanics had a significantly increased rate of change on their SyMS compared to Whites.

4. Discussion

Our patient sample was quite similar to contemporaneous studies from other US specialized centers (Rotstein et al., 2015, Cree and Gourraud, 2016): nearly three out of four patients were women, average age at examination was in early forties, median disability was very mild, and by far the most common disease subtype was relapsing-remitting. One point of difference is that our patients were more racially diverse,

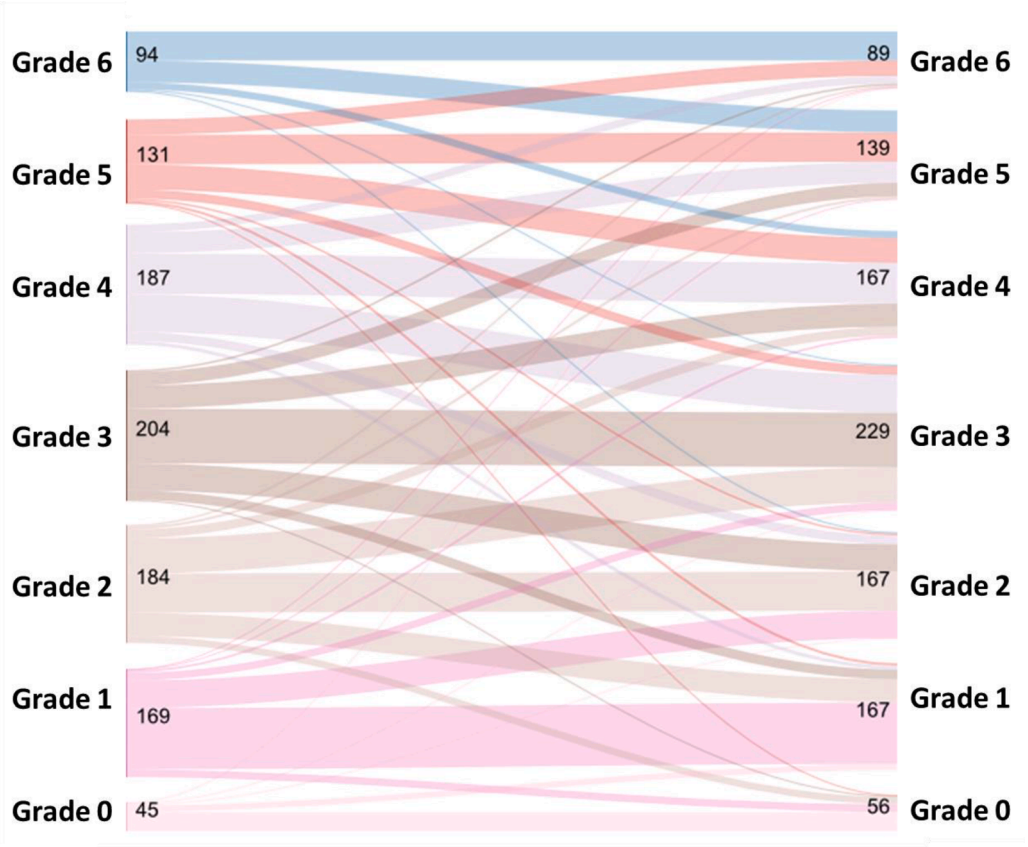

Fig. 2. The Sankey diagram of symptom variability during follow up.
Legend: The Sankey diagram shows number of patients in each grade at baseline (on the left) and at the last follow up (on the right), as well as the 'flow' of patients across severity grades during follow up. Widths of streamline is proportional to number of patients.

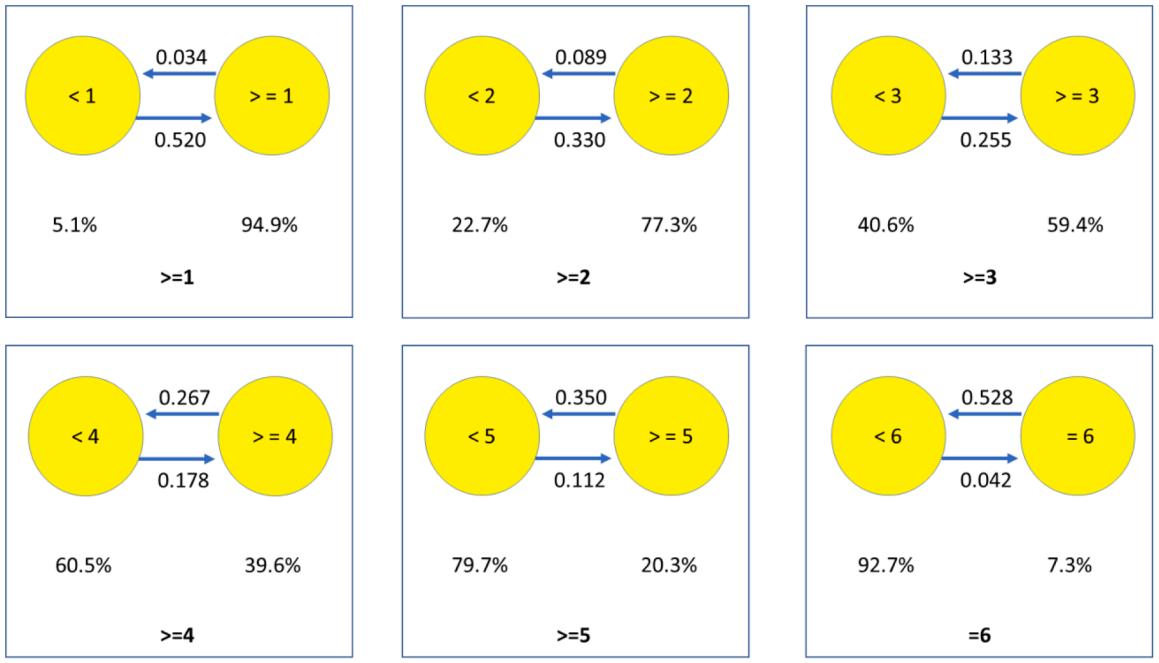

Fig. 3. Probabilities of progression or regression over the course of first year of follow up.
Legend: Probabilities that patient domain scores progressed above a specified threshold over the course on the first year of follow up in any one domain, or regressed below this same threshold.

with nearly 40% being non-White.

Although the median composite SyMS in our sample was 1, corresponding to 'very mild limitation' (i.e. patients make only minor adjustments in everyday functioning), 39% of patients reported symptom severity in at least one domain of sufficient magnitude to force them to give up at least some of their customary activities (score of 4 or more). Among patients over the age of 60, the majority of patients (55%) recorded a score of ≥4 in at least one domain. In comparison, in Sonya Slifka Longitudinal Study of more than 2,000 MS patients with mean age of 51 years, 63% needed help with routine or instrumental activities of daily living (Minden et al., 2006). Comparison between the Slifka study and ours is difficult because the two studies used different scales to assess functional limitations, and had different age distributions and MS criteria, but the degree of functional impairment appears to be higher in the Slifka study, which predates ours by more than 15 years. This may be due in part to the lessening of MS-related disability with calendar time as documented in multiple cohorts (Kister, 2019). Yet, even in the current era, the impact of MS is very considerable in the majority of aging patients.

At baseline and at last followup, the domain with the highest mean score and the highest percentage of patients with severe score (≥4) was fatigue. Fatigue is consistently rated amongthe most pervasive and disabling symptom in MS (de Sa et al., 2011, Nagaraj et al., 2013, Bakshi, 2003, Rommer et al., 2019, Rosenthal et al., 2020). Fatigue scores in our study correlated weakly with age (r=0.108) and disease duration (r=0.114), and much more robustly with disability (r=0.515), suggesting that fatigue is in large parta consequence of disability. One caveat to the above conclusion is that the term 'fatigue' was left undefined in SymptoMScreen, and we therefore not able to discriminate between "fatigue to refer to subjective sensations and fatigability to refer to objective changes in performance" (Kluger et al., 2013). Patients (and clinicians) often conflate these different concepts. Distinguishing one from the other would require a structured examination of all patients to document objective decrements in motor performance, which was not part on our study design. Future studies should examine the relation between fatigue and fatigability and the various variables, such as age and disability, and determine whether fatigability shows a stronger correlation with disability than fatigue.

The other two domains with high proportions of patients who scored ≥4 were ambulation and pain. Patients viewed their physical symptoms (walking difficulty) and 'invisible' symptoms (fatigue, pain) as having a similarly disabling effect on their day-to-day functioning, and both were reasonably correlated with global disability (r approximately 0.50). This is an important message for clinicians who tend to overemphasize motor disability at the expense of the 'intangible' factors, such as vitality, mental clarity, pain and emotional well-being when assessing the effect of the disease on the patient (Barin et al., 2018, Heesen et al., 2018, Ysrraelit et al., 2018).

During the (mean) 21-months followup, overall SyMS score increased modestly but significantly, as would be expected in a slowly progressive disorder. Baseline SyMS scores were highly correlated with followup scores, i.e. high symptom burden at baseline was a strong predictor of high symptom burden at followup, but the correlation was no longer significant after adjusting for the followup time. High degree of variability in symptom botheration can be appreciated from the Sankey diagram (Fig. 2) and the tabulation of probabilities of progression or regression beyond prespecified thresholds over a one-year period (Fig 3). Similarly high degree of individual symptom variability were recorded in a large Australian MS Longitudinal Study, in which overall symptom botheration – assessed with multi-domain MS Symptom Scores (MSSymS), which is quite similar in structure to SyMS - did not change over a one-year period, yet 61-72% of participants reported ≥1-point change in either direction on MSSymS (Zhang et al., 2019). The more extreme domain scores tended to resolve with time, perhaps because the more potent botheration resolves spontaneously or with treatment, because of regression to the mean, or because random errors in category where measurement error in the high or low direction are corrected on subsequent evaluations.

Symptom severity across most domains tended to increase with time, but significance was only reached for dexterity, bladder, vision and pain domains. One exception was anxiety, which trended downwards with time, perhaps reflecting psychological adjustment to disease, or treatment effect. A similar trend for decreasing anxiety over time was also reported in a population-based MS cohort (Wood et al., 2013). A decrease in non-painful sensory symptom botheration could be attributed to physiologic or psychologic habituation or treatment effect. Depression scores remained essentially unchanged in the short-term, in line with what has been observed in some of the prior studies (Bruce and Arnett, 2008, Schreurs et al., 2002).

Our limitation of our study is that we did not collect clinician-rated outcome measures. Composite and domain SyMS scores have been previously validated against clinician-rated measures in cross-sectional samples (Fitzgerald et al., 2019, Meca-Lallana et al., 2020, Kister et al., 2019), but not longitudinal samples. It would be of interest to understand whether changes in patient-reported outcomes correlate with changes in the neurologic examination and other objective tests. Another limitation is that we did not track start and stop dates of the medications and so are not able to comment on whether improvement or worsening of symptoms may have been iatrogenically-induced (Rommer et al., 2019, Frahm et al., 2019), Third, various selection biases could skew results in either direction. On the one hand, the more symptomatic patients may be more likely to attend a specialized center and come more frequently for their appointments; on the other hand, the most disabled patients may be less likely to travel long-distance to a specialized center and less likely to followup. The net effect of such biases could not be assessed and our results must therefore be interpreted with the caveat that they apply to the patients followed in specialized MS centers. Finally, the mean followup of the study was only 2.1 years; conclusions may be different had the cohort were followed for a substantially longer period.

Our work addresses an important and understudied question of symptom evolution in MS. We show that symptoms severity across most domains increases slightly year-to-year, but there is also a high degree of inter-individual variability, with the more extreme scores tending to resolve over time. Higher disability at baseline correlated strongly with overall symptom burden at baseline (composite SyMS score) and weakly predicted an increase in the composite SyMS score during followup.

Data statement

Anonymized dataset is available to qualified researchers upon request.

Disclosures

The study was supported by an unrestricted investigator-initiated grant from Genentech.

IK served on the scientific advisory board for Biogen Idec, and Genentech; received consulting fees from Roche; and received research support from Guthy-Jackson Charitable Foundation, National Multiple Sclerosis Society, Biogen Idec, Serono, Genzyme, and Genentech.

TB has nothing to disclose.

GC: Data and Safety Monitoring Boards: Avexis Pharmaceuticals, Biolinerx, Brainstorm Cell Therapeutics, CSL Behring, Galmed Pharmaceuticals, Horizon Pharmaceuticals,Hisun Pharmaceuticals, Mapi Pharmaceuticals, Merck, Merck/Pfizer, Opko Biologics, Neurim, Novartis, Ophazyme, Sanofi-Aventis, Reata Pharmaceuticals, Receptos/Celgene, Teva pharmaceuticals, Vivus, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee). Consulting or Advisory Boards: Biogen, Click Therapeutics, Genzyme, Genentech, GW Pharmaceuticals, Klein-Buendel Incorporated, Medimmune, Medday, Novartis, Osmotica Pharmaceuticals, Perception Neurosciences,

Recursion Pharmaceuticals, Roche, Somahlution, TG Therapeutics. Dr. Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL.

CRediT authorship contribution statement

Ilya Kister: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft, Writing - review & editing. **Tamar Bacon:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing - review & editing. **Gary R. Cutter:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing - original draft, Writing - review & editing.

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