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Patient-reported outcomes are worse for progressive-onset MS than relapse-onset MS, particularly early in the disease process

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Running title: Progressive-onset MS is more severe in patient-reported outcomes

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Abstract

Background

Treatments for progressive-onset multiple sclerosis (MS) are lacking. To improve the disease management for progressive-onset MS, we examined the differences between relapse-onset MS and progressive-onset MS in patient-reported disability, progression and symptoms.

Methods

1,985 participants of the Australian Multiple Sclerosis Longitudinal Study (AMSLS) were included. Associations between onset-type and outcomes were assessed with negative binomial regression.

Results

The severity of 17 of the 19 outcomes was significantly higher for progressive-onset MS patients than relapse-onset MS patients, including perspectives from disability, progression over the last year, fatigue, sensory, walking difficulties, pain, balance, spasticity, sexual dysfunction, bladder, bowel, anxiety, depression and EQ-5D ($p < 0.05$, adjusted mean ratio ranged from 1.11 to 1.52). The differences between the two onset types was most pronounced early in the disease process and reduced with increasing MS duration, and the interaction was significant for disability, progression over the last year, walking difficulties, bladder problems, bowel problems and spasticity.

Conclusion

Participants with progressive-onset MS were significantly worse off on nearly all patient-reported outcomes than relapse-onset MS participants and the differences were most pronounced early in the disease course, highlighting the importance of early intervention for those with progressive-onset MS.

Introduction

Multiple sclerosis (MS) can be clinically divided into relapse-onset MS, which starts with acute neurological impairment followed by complete or partial remission, and progressive-onset MS, which starts with a progressive phase without relapses or remissions(1). There are certain clinical differences between relapse-onset and progressive-onset. For example, the female : male ratio is much closer to 1:1 in progressive-onset MS(2), and the latitudinal gradient is absent(3, 4) and the mean age at onset is around 9-10 years later(5). Also, the

pathophysiology may be somewhat different, with more diffuse axonal degeneration in progressive-onset rather than inflammatory demyelinating lesions as seen in relapse-onset MS, although this remains controversial(6).

In recent years, dramatic progress has been made in understanding relapse-onset MS, in terms of risk factors and therapies(7, 8), but similar knowledge of progressive-onset MS is quite sparse. Only one treatment, ocrelizumab, has recently been shown as being effective in reducing disability progression and MRI changes in patients with primary progressive MS(9). The limitations in understanding progressive-onset MS are partly due to the low numbers of people with this phenotype (~12% of MS)(10), which has prevented separate sub-type analyses in most observational and clinical trial studies due to insufficient power. In addition, the typical study duration of 2-3 years is probably insufficient to reliably measure disability progression. Although the Expanded Disability Status Scale (EDSS) is often used as a primary outcome measure in clinical trials, it is strongly determined by ambulation and lacks sensitivity and specificity(11). While MRI parameters and biomarkers are of great interest, their correlation with clinical disability or symptoms is moderate(11).

Defining differences between the two onset types may be the first step in clarifying the underlying mechanisms of progressive-onset MS as compared to relapse-onset MS. As reducing symptoms severity and enhancing quality of life are the ultimate goals of progressive-onset MS management, patient-reported outcome measures have become an increasingly important field of research(12). There are several large studies(13, 14) that have looked at those measures, but they examined them by disease type(1) rather than onset type. Differences by disease type may reflect the effects of disease duration, age, and age-associated comorbidities instead of true differences between onset types. Therefore, it is our aim to examine differences between progressive-onset MS and relapse-onset MS in relation to disability, disability progression, symptom severity and quality of life based on patient-reported outcomes.

Methods

Participants

The study sample was recruited from the Australian Multiple Sclerosis Longitudinal Study (AMSLS) database. The AMSLS participants have been shown to be representative of the

Australian MS population, and has an estimated 96% of participants diagnosed with definite MS according to the McDonald criteria(15). Recruitment to the AMSLS is ongoing to counter the attrition rate and is being undertaken with the assistance of all Australian State and Territory MS Societies. Written informed consent forms for the survey were provided by each participant. Ethical approval for the study was originally granted by the Australian Capital Territory HREC, and in 2014 by the Tasmanian Health and Medical HREC after the study centre was relocated to Tasmania.

Survey and respondents

All 3,208 active AMSLS participants were invited to complete the 2015 Medication and Disease Course Survey (2,179 invitations for the online survey, 1,029 for the paper survey determined by participant preference). Of those, 1,985 (62%) completed the survey (1,459 online, 526 paper).

Outcome measures

In total, 19 patient-reported outcomes were recorded in the survey. The Patient-Determined Steps Scale (PDDS) measures mobility across nine levels and correlates highly with EDSS ($r=0.78(16)$). The Fatigue Severity Scale (FSS) is a commonly used patient-reported measurement to assess fatigue in the preceding week (mean of 9 items (1-7 scale))(17). Anxiety and depression was assessed by the Hospital Anxiety and Depression Scale (HADS)(18) (total score of 14 items (1-4 scale). The European quality of life (EQ-5D) assessed health-related quality of life (5 items, 1-5 scale, converted to a utility score from 0 (death) to 1 (perfect health))(19).

The remaining 14 outcomes were assessed with one single numeric rating item from 0 (no problems/progression) to 10 (worst possible symptoms/progression). Participants rated the speed of progression by which their MS progressed over the previous 12 months. The severity of 13 symptoms (walking difficulties, difficulty with balance, fatigue, bladder problems, sexual dysfunction, spasticity, sensory symptoms, bowel problems, pain, feeling of depression, cognitive symptoms, feeling of anxiety and vision problems) was rated by comparing to before they developed MS.

Other measures

MS onset type was derived from their reported MS type: Primary Progressive MS (PPMS), Relapsing Remitting MS (RRMS), Secondary Progressive MS (SPMS), Progressive Relapsing MS (PRMS) and unsure. Progressive-onset type included PPMS and PRMS, while

relapse-onset type included RRMS and SPMS. MS onset type was also assessed by a physician between 2002-2006 on a subset of participants (n=1,089), and a further subset (n=370) had two physician reports. The measures of agreement between patient-reported and physician-reported onset type (% agreement 89.7%; kappa 0.53) were similar to the measures of agreement between physicians where two physician reports were completed (% agreement 90.0%; kappa 0.51). Other demographic characteristics included were sex, date of birth, year of diagnosis and highest education level.

Data analysis

Association were evaluated using negative-binomial regression. To confirm the robustness of our conclusions to the choice of statistical model, we also estimated the associations using alternative regression techniques: linear regression with transformation of the outcomes scores (severity of fatigue, sensory symptoms, fatigue severity scale, HADS-Anxiety and HADS-Depression), Cragg hurdle regression (zero-inflated pain and sexual dysfunction scores), or tobit regression (right-censored EQ-5D scores). The findings were not materially altered by the use of these alternative statistical models.

For each outcome, we identified potential confounders using causal diagrams and examined whether the coefficient of the binary covariate for MS onset type was altered by more than 10% when a covariate for the confounder was added to the model. Statistical interaction was assessed by a Wald test of the coefficient of a covariate formed as the product of the binary covariate for MS onset type and the covariate for the putative modifier. STATA (version 14; StataCorp LP, College Station, TX) was used for all data analysis.

Results

Of all participants, 11.6% had progressive-onset MS (Table 1). Among those who were unsure and had a physician MS type diagnosis (n=145), 11.0% had progressive-onset MS. The mean age of progressive-onset participants was 8 years higher than relapse-onset participants. When comparing those who responded to this survey round to those who did not, we found similar distributions by sex (p=0.47) and disease duration (p=0.08). However, responders were older at participation (+2.2 years, p<0.001), and diagnosis (+1.6 years, p<0.001), and had a higher education level (+0.1 unit (on a scale from 1-5), p=0.003).

For all outcomes, mean values were worse for progressive-onset MS participants (Table 2). Among progressive-onset cases, the symptom with the highest mean value was walking difficulties (6.82), while among relapse-onset MS, the highest mean value was seen for fatigue (4.94). For both onset types, vision problems had the lowest mean value. In univariable analyses, the mean severity was significantly higher for those with progressive-onset MS compared to those with relapse-onset MS for most outcomes. The strongest association was for PDDS, where the mean level of walking difficulties for progressive-onset MS patients was 1.86 times greater than those of relapse-onset MS. After adjusting for confounders, magnitudes of the effect were reduced somewhat for most outcomes, but remained significant. The magnitudes of effect for anxiety and depression increased because of negative confounders (e.g. HADS-Depression: age; HADS-Anxiety: sex, age, age of diagnosis and MS duration), which made the association significant for HADS-Anxiety. No differences were seen for cognitive symptoms or vision problems.

We next examined whether there were interactions by sex, age, age of diagnosis or MS duration. We identified a consistent pattern of interaction with MS duration, where the difference in outcomes between progressive-onset and relapse-onset was particularly pronounced for those who were still early in the disease process and the difference was attenuated for those who had had MS for longer at the survey time. This pattern was statistically significant for walking difficulties, bladder problems, spasticity, bowel problems, progression over the last year and disability level (Figure). For those with progressive-onset MS, the outcome severities were already high early in the disease course with relatively little increase over time after that. For those with relapse-onset MS, the severity was low early in the disease course and increased more strongly over time.

We had some concern that people with progressive onset MS had a delayed MS diagnosis which could partly explain a higher outcome severity early in the disease process. On a sample of 1628 AMSLS patients, we had data on both the year of first symptom and the year of diagnosis. The gap between the year of first symptom and the year of diagnosis was similar for both onset types (5.4 ± 7.0 years for progressive-onset, and 4.6 ± 6.8 years for relapse-onset; $p=0.14$ for test of difference).

As those with PRMS may be different to those with PPMS, we repeated the analysis excluding PRMS participants (Supplementary Table 1). The symptom severity of those with PPMS was generally similar to those with PRMS, although the mean severity was somewhat

lower for PPMS in some symptoms, resulting in slightly lower effect sizes when compared to with relapse-onset participants (e.g. sensory symptoms, pain, HADS-Anxiety). This supported the inclusion of PRMS cases with PPMS cases in this analysis.

Discussion

In this large national sample of Australians with MS, we found that people with progressive-onset MS were significantly worse-off for nearly all patient-reported outcomes after accounting for confounding factors like age and disease duration, and the differences were most pronounced early in the disease course, highlighting the importance of early intervention in for those with progressive-onset MS.

This is the first study focusing on the comparison of symptoms and disability between progressive-onset MS and relapse-onset MS from the patients' perspective. Studies showed that people with progressive-onset MS were worse off in terms of disability as measured by EDSS, Multiple Sclerosis Severity Score and PDDS, but they often compare MS types, rather than onset types. Age and disease duration are important confounders in these associations and need to be carefully taken into account in such cross-sectional comparisons(20). We found that even after taking confounding factors into account, the severity of outcomes in those with progressive-onset MS was significantly worse than those with relapse-onset MS for all outcomes, except cognitive function and vision problems. For example, compared to those with relapse-onset MS the mean severity for progressive-onset MS was 1.52-times higher for walking difficulties.

Importantly, we also found that the differences in outcomes were most pronounced early in the disease course, this interaction being significant for six of the outcomes. This is consistent with some indirect evidence in the literature regarding disability. For example, PDDS-measured disability in cases with PPMS was significantly higher than those with SPMS, and the difference decreased with increasing disease duration(20). The rate of disability accumulation was similar between relapse-onset MS and progressive-onset MS when using higher EDSS milestones (such as from EDSS 6 to 8)(21, 22). This has raised the argument that progressive-onset and SPMS are the same or at least have the same mechanisms of disease progression(23).

Our findings show that the work should not only focus on disease-modifying treatments, but also on symptomatic management. The assessment and management of specific symptom in patients with MS is complex and multifaceted, with different symptoms influencing each other. For example, treatment of pain in MS often utilises CNS active drugs such as pregabalin or carbamazepine(24, 25), both of which can worsen cognition. Similarly, the treatment of bladder hyperactivity with anticholinergics can worsen constipation and cognition(26). Our work also clearly demonstrates the need for early interventions. Clinical trials in progressive MS patients should have a specific focus on early MS, as gain could be made by earlier intervention to reduce the total burden of progressive MS. A recently published successful trial in PPMS included patients where substantial disability had already accrued (EDSS 3.5-6.5),(9). Indeed, the mean disease duration since symptom onset was 6 years in this trial,(9) suggesting that there is the potential to treat earlier in the disease course. The focus on early interventions aligns with the use of immunotherapy treatments in those with relapsing-onset MS, where it has been shown that early treatment seems to substantially benefit outcomes compared to delayed treatment.

A key strength of this study is that the AMSLS is a large representative dataset with a sufficient number of people with progressive-onset MS to obtain reliable estimates. One limitation was that we had a moderate response rate, which may result in selection bias. Those who responded had a slightly higher age, age of diagnosis and higher education level, but the differences were not large relative to the total variation in the sample. Our cohort was somewhat more female dominated, possibly reflecting a lower male engagement in studies such as these. However, sex was not a major driver of most outcomes, and was adjusted for if it were a confounder (e.g. sexual dysfunction, HADS-anxiety) and therefore did not bias our reported outcomes.

The validity of the assessment of onset type was high (89.7% agreement). However, if we were able to remove this measurement error, associations may have even been stronger. Despite 11.7% of participants selecting “unsure” for their disease type, which reduced our sample size, it left us with a sample in whom we are relatively confident about their onset phenotype, therefore reducing measurement error. In addition, among those unsure cases (n=145) who had physician reports done, 11.0% had progressive-onset MS, suggesting this group had a similar distribution in onset type compared to the rest of our dataset (11.6% progressive-onset MS). We had some concern that patients with progressive-onset had a delayed diagnosis, possibly contributing to a worse outcome severity in early MS, however

the gap between the year of first symptom and the year of first diagnosis was similar in both onset types.

In conclusion, our study highlights the need to identify disease modifying and symptomatic treatments and to test treatments early in the disease process.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Table 1. Demographic characteristics of patients with distinct MS onset types

		Progressive-onset	Relapse-onset	Unsure
Total ^a , n (%)	1,985	231 (11.6)	1,514 (76.3)	233 (11.7)
Sex, n (%)				
Male	435 (21.9)	85 (36.8)	279 (18.4)	68 (29.2)
Female	1,549 (78.1)	146 (63.2)	1,234 (81.6)	165 (70.8)
Male : Female ratio	1 : 3.6	1 : 1.7	1 : 4.4	1 :2.4
Age (years), mean ± SD	55.3 ± 11.3	61.8 ± 9.6	53.5 ± 11.0	59.8 ± 11.2
Age of diagnosis (years), mean ± SD	41.3 ± 10.6	46.5 ± 11.1	40.2 ± 10.2	42.6 ± 11.3
Disease duration (years), mean ± SD	14.1 ± 8.8	15.3 ± 9.4	13.4 ± 8.1	17.3 ± 11.3
Education level, n (%)				
Primary school or Secondary	577 (29.1%)	93 (40.4%)	393 (26.0%)	86 (36.9%)

school

Occupational certificate or

diploma 696 (35.1%) 79 (34.3%) 529 (35.0%) 87 (37.3%)

University bachelor's degree 415 (21.0%) 36 (15.7%) 342 (22.6%) 37 (15.9%)

University postgraduate degree 294 (14.8%) 22 (9.6%) 248 (16.4%) 23 (9.9%)

Employed ^b (n (%)) 807 (50.5%) 39 (28.3%) 700 (54.0%) 67 (41.9%)

a: MS onset type was missing for 7 participants.

b: Included respondents of working age (age of 65 years) (n=1598).

Table 2. The mean severity and the mean ratio between the two MS onset types

	Mean values of different MS onset types ± standard deviation		Progressive-onset MS vs relapse-onset MS			
	Progressive-onset MS	Relapse-onset MS	Unadjusted mean ratio (95% CI)	p-value	Adjusted mean ratio* (95% CI)	p value
Symptom severity^a (0-10)						
Walking difficulties	6.82 ± 2.97	3.89 ± 3.17	1.75 (1.56-1.97)	<0.001	1.52 ^b (1.36-1.70)	<0.001
Difficulty with balance	6.45 ± 2.93	4.13 ± 3.01	1.56 (1.41-1.73)	<0.001	1.37 ^b (1.24-1.51)	<0.001
Fatigue	5.83 ± 2.60	4.94 ± 2.72	1.18 (1.09-1.27)	<0.001	1.12 ^b (1.04-1.22)	0.003
Bladder problems	5.61 ± 3.29	3.92 ± 3.25	1.43 (1.26-1.62)	<0.001	1.28 ^b (1.13-1.45)	<0.001
Sexual dysfunction	5.40 ± 3.75	3.38 ± 3.45	1.60 (1.35-1.88)	<0.001	1.31 ^c (1.11-1.54)	0.002
Spasticity	5.25 ± 3.09	3.32 ± 2.99	1.58 (1.38-1.81)	<0.001	1.45 ^b (1.26-1.66)	<0.001
Sensory symptoms	5.07 ± 2.94	4.36 ± 2.79	1.16 (1.06-1.27)	0.002	1.12 ^b (1.02-1.23)	0.022
Bowel problems	4.41 ± 3.05	3.02 ± 3.07	1.46 (1.25-1.70)	<0.001	1.31 ^b (1.12-1.53)	0.001
Pain	3.98 ± 3.07	3.10 ± 2.97	1.28 (1.11-1.49)	0.001	1.18 ^d (1.01-1.38)	0.037
Feelings of depression	3.93 ± 2.92	3.12 ± 2.78	1.26 (1.10-1.44)	0.001	1.32 ^e (1.15-1.52)	<0.001
Cognitive symptoms	3.84 ± 2.88	3.56 ± 2.65	1.08 (0.97-1.21)	0.180	1.08 ^f (0.96-1.21)	0.205
Feelings of anxiety	3.70 ± 2.92	3.09 ± 2.73	1.20 (1.05-1.37)	0.008	1.23 ^d (1.07-1.41)	0.004
Vision problems	2.67 ± 2.86	2.33 ± 2.51	1.14 (0.97-1.35)	0.110	1.12 ^f (0.94-1.32)	0.205
Progression over the 12 months (0-10)	3.47 ± 2.71	2.09 ± 2.32	1.66 (1.44-1.92)	<0.001	1.48 ^b (1.28-1.72)	<0.001
Patient Determined Steps Scale (0-8)	4.66 ± 2.28	2.50 ± 2.23	1.86 (1.66-2.09)	<0.001	1.57 ^b (1.40-1.76)	<0.001
Fatigue Severity Scale (0-7)	4.67 ± 2.04	4.14 ± 2.06	1.13 (1.06-1.20)	<0.001	1.11 ^b (1.04-1.18)	0.003
HADS-Anxiety (0-21)	7.30 ± 4.59	7.02 ± 4.17	1.04 (0.95-1.14)	0.375	1.11 ^g (1.01-1.22)	0.029
HADS-Depression (0-21)	6.87 ± 3.74	5.35 ± 3.65	1.28 (1.17-1.41)	<0.001	1.25 ^b (1.13-1.38)	<0.001
EQ-5D^h (0-1, from dead to perfect health)	0.54 ± 0.27	0.73 ± 0.22	0.74 (0.62-0.90)	0.002	0.79 ^b (0.65-0.95)	0.014

a: Symptoms are ordered from most severe to least severe according to the progressive-onset MS group;

b: adjusted for age;

c: adjusted for sex and age;

d: adjusted for age and age of diagnosis;

e: adjusted for age of diagnosis;

f: adjusted for age, age of diagnosis and MS duration;

g: adjusted for sex, age, age of diagnosis and MS duration;

h: 29 values of EQ-5D was negative, which means these patients were worse than dead. To do the analysis, these values were replaced with “0”.

Bold values indicate significance ($p < 0.05$);

Figure. Associations between MS duration and severity of outcomes for those with progressive-onset MS (orange bars) and relapse-onset MS (blue bars), showing that the difference between the two onset types was particularly pronounced early in the disease process and diminished over time (p-values for interaction provided between brackets).

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