The role of specialist nurses in detecting spasticity and related symptoms in multiple sclerosis.

Abstract

Background: Spasticity is a frequent symptom of multiple sclerosis (MS), which may influence negatively daily living activities (ADL).

Objectives: To (1) explore the feasibility to conduct a structured interview by specialist nurses about limitations in ADL; (2) determine the percentage of people with MS (PwMS) with limitations in ADL related to spasticity; (3) to assess the knowledge about spasticity and describe its clinical features.

Design: Observational, cross-sectional, multicentre study in 16 MS units of Catalonia (Spain). Participants were recruited from the outpatient facility and day-care hospital between July 2018 and June 2019 and met the following criteria: 1) age 18 or older, 2) diagnosis of MS according to McDonald criteria 2010 and 3) no clinical relapse in previous 30 days.

Methods: Specialist nurses conducted a structured interview divided in two parts: the assessment of (1) limitations in the ADL and (2) the presence of spasticity and associated symptoms. The usefulness of this intervention was requested. This study met the STROBE reporting guidelines checklist for observational studies.

Results: 368 pwMS (244 women) with a mean age of 46 years and a median Expanded Disability Status Scale score of 2.5 (range, 0-8.5) were included. 262 (71%) pwMS had limitations in the ADL, and spasticity was reported as the most limiting symptom in 59 (23%). As a result of the interview, spasticity was observed in 199 (76%) participants; 47

(24%) of them were unaware that they had spasticity, and 102 (51%) would not have reported it spontaneously. The level of the interview satisfaction was high (90%).

Conclusions: Spasticity is a complex and limiting symptom in MS. The structured interview conducted by specialist nurses is feasible and has good acceptance.

Patient contribution: Specialist nurses can be proactive in MS clinical assessment, which may help to detect symptoms with negative impact on quality of life.

What does this paper contribute to the wider global clinical community?

What is already known about the topic?

- Spasticity is a highly prevalent symptom in people with multiple sclerosis (pwMS) and exerts an influence in lower limb function and gait.
- There is an increasing demand from pwMS to improve the management of symptoms in their daily lives.
- MS specialist nurses provide specific medical education, but its role in the diagnosis and clinical approach to MS symptoms is not well established.

What this paper adds

- Nurse-led spasticity-related symptom interviewing is feasible and may help detect unmet needs in pwMS who do not ask about such symptoms.
- PwMS perceive spasticity as one of the most limiting symptoms for activities of daily living (ADL) and is associated with a worse perception of quality of life (QoL).

Keywords

Limiting symptoms; Multiple Sclerosis; Quality of life; Spasticity; Specialist nurses.

Background

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system with an autoimmune origin. It is the leading cause of non-traumatic disability in young adults, with a direct impact on autonomy, functionality to perform activities of daily living (ADL) and quality of life (QoL) (Browne et al. 2014; Kister et al. 2013). Lower limb function is given the highest priority in people with MS (PwMS) followed by visual functioning and cognition, especially in longer lasting MS (Heesen et al. 2008; Larocca 2011). Spasticity is a highly prevalent symptom in MS and exerts an influence in lower limb function and gait. The diagnosis and approach to spasticity is complex both due to its heterogeneous presentation and the association with sphincter disorders, fatigue and/or sleep disturbances that may obscure its clinical expression at the beginning (Flachenecker et al. 2014). Early detection and proper management of spasticity are essential to preserve QoL and to reduce the associated socioeconomic burden in MS. This fact is especially important in the advanced stages of the disease, since it causes an increase of both the use of health resources and the physical and emotional burden of the family members and caregivers (Oreja-Guevara et al. 2013).

The role of specialist nurses has grown dramatically in the past 10 years. In addition to providing the usual care to pwMS, specialist nurses are in charge of coordinating care, providing specific medical education, and being the reference of the medical team for solving doubts (Biswas et al. 2019; Mancini et al. 2020). Their role in the diagnosis and clinical approach to symptoms may not be completely developed yet, but there is growing evidence that their behavioral characteristics may influence the management of pwMS (Fernández-Pablos et al. 2016; Saposnik et al. 2021). Importantly, they can capture the perception of their symptoms more closely. The aims of this study were: 1) explore the feasibility to conduct a structured interview by specialist nurses about

limitations in ADL; 2) to determine the percentage of pwMS with limitations in ADL related to spasticity; 3) to assess the knowledge about spasticity and describe its clinical features in a group of pwMS.

Material and methods

Sample Description

This was an observational, descriptive, cross-sectional multicentre study which included pwMS from sixteen MS units from Catalonia (Spain). All participants were prospectively selected from July 2018 to June 2019 from the outpatient facility and day-care Hospital of Neurology if they fulfil the following inclusion criteria: 1) age 18 or older and; 2) diagnosis of MS according to the Mc Donald criteria 2010 (Polman et al. 2011); 3) absence of clinical relapse in the 30 days prior to study inclusion. All investigators were given the study protocol which was approved by the clinical ethical committee of the Hospital Clinic (HCB/2018/0186) and by the rest of the clinical ethical committee of the participating centres. This study was performed in accordance with the ethical standards of the Helsinki Declaration (1964) and its later amendments. All participants provided their written informed consent before enrollment onto the study.

Procedures

The principal investigators developed a structured interview script to find out the limitations that patients had in activities of ADL, their perception of QoL, and if they had symptoms of spasticity or other related symptoms, considering the lack of availability of a validated questionnaire to obtain this information in a simple and reproducible way (Oreja-Guevara et al. 2013; Fernandez et al., 2020)". The structured script was sent to all

collaborators and discussed in a presential meeting. After reviewing the initial draft and including several subsequent iterations via electronic communication, the latest version was administered to 10 pwMS from Hospital Clinic of Barcelona, to ensure that it was feasible, and that the structured interview could be carried out in a reasonable amount of time for clinical practice. Afterwards, the final version was sent to the centres. Every 3 months, the principal investigators contacted all collaborators for technical support. Each centre's nurses performed one structured interview (Table 1) per participant, without limitation on the number of participants to include during the recruitment period. Each centre and participant were identified by a number following the recruitment order, in compliance with the General Data Protection Regulation of May 25, 2018. Once the recruitment period ended, the coordinating investigator from each centre sent all the anonymously completed forms to the principal investigators at the Hospital Clínic by post. This study met the STROBE guidelines for reporting observational studies (Supplementary file 1).

Interview Description

The clinical interview consisted of a collection of demographic and clinical variables such as age, sex, date of diagnosis, degree of disability measured by the Expanded Disability Status Scale (EDSS) (Kurtzke et al. 1983) among others (Table 2). The clinical interview lasted for 20-30 minutes and was divided into two parts. First, we asked the participants if there were any symptoms related to MS that limited the ADL, and the perception of health status (EQ-VAS), the latter being part of the scale of 5-item QoL (EQ5D) (Devlin et al. 2018). The second part consisted of a series of questions related to spasticity and associated symptoms which was completed only if the participant reported symptoms suggestive of spasticity; it registered the presence of stiffness, muscle cramps and spasms, urinary disorders, sleep disturbances, fatigue and mood disorders

(Fernandez et al. 2020; Oreja-Guevara et al. 2013). Participants were also asked about the current amount of physical activity. The frequency and presence of pain were assessed via a 0-10 visual analogue scale (VAS) (0 being absence of pain, 10 excruciating pain). Spasticity was determined using the 0-10 points numeric rating scale (NRS) (Farrar et al. 2008), where 0 means absence of spasticity and 10 the worst possible spasticity. Finally, the participants were asked about the usefulness of the structured interview, and whether he/she would have mentioned the spasticity symptoms spontaneously if the nurse had not asked them.

Statistical methods

Among all structured interviews collected, only those with complete information regarding limitation in ADL and symptoms related to spasticity were included in the analysis by principal investigators. Descriptive statistics were computed as mean (standard deviation, SD) unless otherwise noted. We classified participants based on their response to the presence of limiting symptoms related to MS and the presence of spasticity and related symptoms. We defined the presence of spasticity and related symptoms if there were spasticity and/or spasms-cramps with or without any of the other symptoms: pain, bladder dysfunction, sleep disorders and/or fatigue (Fernandez et al., 2020). Differences among groups based on spasticity and/or presence of related symptoms were studied using the $\chi 2$ test, with a significance level set to $p< 0.05$. Binary logistic regression was performed to identify predictors of specific symptoms such as urinary disturbances, fatigue or sleep disturbances that could be spasticity-independent. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc, Chicago, IL) software.

Results

Clinical description of the participants and the interview

Sixteen centres with MS units distributed across the 4 provinces of Catalonia participated in the study. A total of 398 structured interviews were collected, of which 368 were considered valid. Thirty were discarded for the following reasons: 24 did not complete the interview despite the fact that the participant reported a limiting symptom; the remaining 6 were incomplete (Figure 1). The structured interview was administered by MS specialist nurses, and the mean number of valid interviews (range) per centre were 26 (1-18) with mean time (range) needed to carry the interview of 20 (5-40) minutes.

Two thirds of the participants were women (244/368, 66%), with a mean age of 46 (11) years old and a mean disease duration of 9 (9) years. The median EDSS was 2.5 (range, 0-8.5) and 299 interviewees (81%) had relapsing-remitting MS (RRMS), 32 (9%) primary progressive MS (PPMS), and 37 (10%) secondary progressive MS (SPMS). The percentages of participants receiving disease modifying treatments were 94% in the case of RRMS, 54% for SPMS and 78% for PPMS (Table 2). No differences in demographic characteristics (age and sex) were observed in participants among all centres ($p<0.05$; data not shown).

Limitation of daily activity and its causes

Two hundred and sixty-two participants (71%) reported having limitations to accomplish ADL due to MS. The median EDSS was 3.5 (range 0-8.5) and 36 participants (14%) had an EDSS <2. Participants with a limitation in ADL had a worse perception of QoL compared to participants without limitations (EQ-VAS mean = 58 [18] vs 85 [14]; $p <0.001$). The most frequent limiting symptom was spasticity (n = 59, 23%), followed by impaired mobility (n = 55, 21%), weakness (n = 53, 20%), fatigue (n = 52, 20%), balance problems (n = 40, 15%), and others (figure 1). Among those with limiting

symptoms, participants who complained of spasticity had a reduced perception of QoL compared to the other (EQ-VAS = 56 [18] vs 62 [18]; p = 0.05).

Characteristics of spasticity and/or related symptoms

One hundred seventy-one interviewed participants (65%) were aware of the meaning of spasticity, while 74 (28%) were not and 17 (6.5%) did not answer the question. Overall, spasticity and/or the presence of related symptoms was detected in 199 (76%) surveyed participants. Among these, 152 (58%) were aware of the meaning of spasticity and 103 (52%) were told by the referred physician. Participants with spasticity and/or related symptoms had a higher EDSS (median [interquartile range] = 4.0 [2.5-6.0] vs 2.5 [1.5-3.5]; p <0.001), and were not working in a higher proportion as well (33 [19 %] vs 3 [6%]; p = 0.03). The duration of spasticity and/or related symptoms was 70 (92) months.

The average subjective perception of spasticity measured by the numerical rating scale (NRS) was 3.9 (7.8), and the average perception of related pain measured by the 0-10 VAS was 4 (8). Stiffness was the most prevalent symptom (n = 181, 91%) followed by muscle spasms (n = 142, 71%) and cramps (n = 134, 68%). One hundred and fifty-five participants presented urinary disturbances, being daily urgency and/or incontinence the most frequent (67%). Participants who complained about spasticity had a higher percentage of sleep disturbances (59% vs. 33%, p = 0.003), troublesome in moving in bed (33% vs. 2%; p <0.001), and higher frequency of restless legs syndrome (42% vs. 16%, p = 0.002). Including age, sex, EDSS and disease duration in a multivariate analysis, spasticity was an independent factor for sleep disturbances (odds ratio [OR]=2.63; 95% confidence interval [CI]=1.32-5.33; p=0.006) and restless leg syndrome (OR=3.47; 95% CI=1.46-8.23; p=0.005). Regarding troublesome in moving in bed,

spasticity was considered also an independent factor (OR=12.07; 95% CI=1.57-92.79; p=0.02) in addition to being female (OR=2.42; 95% CI1.17-5.00; p=0.02) and EDSS (OR=1.61; 95% CI=1.34-1.95; p<0.001). Participants who complained about spasticity used hypnotic medicines more frequently (29% vs. 12%; p = 0.02), but they did not differ in terms of having more sphincter problems (79% vs 76%; p=0.60), fatigue (74.3% vs. 10; p=0.28) or mood disturbances (65% vs 52%; p=0.23). One hundred fifty-one (62%) participants practised some type of physical exercise and/or had physical therapy periodically, with an average time invested per week of 4 (3) hours. However, no differences in time spent in physical exercise and/or physical therapy were observed between participants with and without spasticity.

At the time of the interview, 79 (40%) were receiving symptomatic treatment for spasticity (63 as monotherapy and 16 with a combination of drugs, with a mean delay time from the onset of symptoms of 24 (49) months. The mean number of treatments tested in those who started any treatment was 1.5 (0.6), and the average level of satisfaction with the treatment measured with the 0-10 VAS was 5.6 (3.5). The reasons for not starting any symptomatic treatment related to spasticity were lack of prescription by the treating physician (29%), was not consider it necessary (12%), the participant rejected it (2.5%) and 57% was unknown.

Usefulness of using the spasticity structured interview by specialist nurses.

Two hundred and thirty-five participants (90%) found the structured interview useful, only 6 (2%) did not, and the remaining 21 (8%) did not answer. Among those who found it useful, 101 (44%) would have not mentioned the limiting symptoms spontaneously to their physician. Sixty five percent of participants (171 out of 262) knew the meaning of spasticity; of these, 106 (62%) had been informed by their doctor that they

actually had spasticity. Conversely, 47 participants with spasticity (24%) were unaware that they had it, and 24 out of the 47 (51%) would have not asked the doctor spontaneously.

Discussion

The results of this observational study on pwMS' perception show that spasticity is perceived as one of the most limiting symptoms for activities of ADL in MS and that is associated with a worse perception of QoL. Nurse-led spasticity-related symptom interviewing is feasible and may help to detect unmet needs in pwMS who do not ask about such symptoms.

The comprehensive care of pwMS is increasingly complex because it includes the evaluation of clinical and radiological activity, treatment efficacy and safety, the assessment of disability status and other related symptoms, such as spasticity. Most clinicians have to prioritize the evaluation of disease activity and disability over the others due to the lack of time in clinical settings. However, there is an increasing demand from pwMS to improve the management of symptoms in their daily lives, especially those with high level of disability (Rønning et al. 2017). However, limitations in ADL can occur in pwMS even with no objective signs of neurological dysfunction. In fact, gait kinematic studies in pwMS without clinical evidence of disability have observed a different gait pattern than healthy subjects, with lesser daily activity measured by accelerometers (Pau et al. 2015; Martin et al. 2006). Therefore, systematic evaluation, even in without objective disability, may help to identify symptoms that are playing a limiting role in ADL.

The perceived frequency of spasticity in our study (76%) indicates that it is a frequently observed symptom in MS (Kister et al. 2013), closely related to gait disorders, and one of the most limiting symptoms for ADL (Rizzo et al. 2004) and QoL

(Flachenecker et al. 2014; Oreja-Guevara et al. 2013). Despite stiffness and spasms were the most common symptoms, 69% complained about 2 or more other associated symptoms. However, spasticity tends to be under-treated (40% in our cohort) but polymedicated with other drugs (eg. hypnotic drugs) and pwMS frequently show a low level of treatment satisfaction (Flachenecker et al. 2014; Oreja-Guevara et al. 2013). The reasons why this may happen are not well understood. A possible explanation may be the lack of an active prescription by the doctor, the fact that a significant proportion of (25%) do not know what spasticity is, and the evidence that a large number of pwMS would not have mentioned this symptom if they hadn't been asked. Recently, a new proposed definition of spasticity has emerged with a broader concept “Spasticity-Plus Syndrome” including spasticity and related symptoms. The intention of this definition is to help healthcare professionals look for the presence and severity of spasticity and other related symptoms and try to manage them in the most appropriate way possible, reducing potential side effects and drug interactions (Fernandez et al., 2020). The relevance of conducting a structured interview may help to detect these pwMS and treat them appropriately.

In the last decade, specialist nurses have participated in clinical management and education of immunomodulatory therapies and are closer to pwMS lives. The creation of a structured interview may be a support strategy to systematically assess spasticity and related symptoms that may interfere with ADL, and promote educational awareness for pwMS (Fernández-Pablos et al. 2016; Currie 2001; Crawford et al 2014; Jarrett 2006).
This study has limitations that are worth to mention. The structured interview lacks of a prior validation because it was created to obtain information about the limiting symptoms associated with MS and QoL on a regular basis through the clinical interview. To ensure this, the original script was reviewed in several rounds, and its viability was confirmed,

and the principal investigators offered technical support to the centres during the study. We cannot rule out that the response has been amplified by awareness of being measured and social desirability; however, PwMS are used to being visited by nurses from specific MS units as part of the normal management of their disease, and they have a very close relationship, a fact that can mitigate it. Finally, the cohort of MS sample of this study is fairly representative of the general MS population, since the inclusion criteria were wide and participants included had similar demographic and clinical features frequently seen in prior research (Flachenecker et al. 2014; Milinis et al., 2016; Oreja-Guevara et al. 2013).

In conclusion, the management of MS has completely changed in the last decade and the active role of the specialist nurses in exploring limiting symptoms such spasticity is feasible and well accepted among pwMS.

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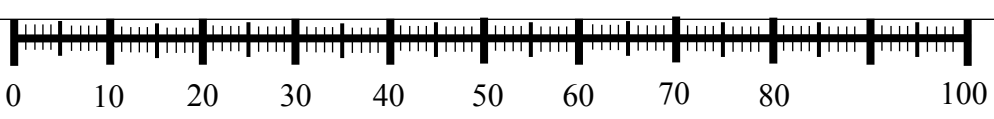
Tables

Table 1. The structured interview for assessing limitations in activities of daily living in people with MS

Demographic data: Age, sex, marital status, current employment and educational level **Multiple sclerosis (MS) data:** MS type / MS diagnosis / EDSS score / Current disease modifying treatment
There are any limiting symptom related to MS that effect your activities of daily living? yes/no **If yes:** Which one? What is the limitation?
We would like to know how good or bad is your health perception today. This scale goes from 0 to 100. One hundred represents the best health perception that you could imagine, and 0 the worst. Select with an X where you believe it suits you and write the number inside the box 

90

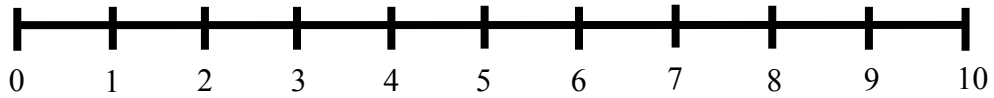
Do you know what is spasticity? yes/no

Do you think you suffer from spasticity? yes/no

Has your doctor ever tell you to have spasticity? yes/no

When did spasticity and related symptoms start?

Spasticity numeric rating scale (0-10):



Are you currently receiving treatment? Which?

- Start date of the first treatment:

- Number of previously used treatments: 0 1 2 > 2

- How satisfied do you feel about treatment of spasticity? (0-10):

Do you have any of the following symptoms?

1. Feeling of stiffness (eg walking / resting), muscle cramps and/or spasms: yes / no

If yes, rate the frequency and pain from 0 to 10:

2. Urinary disorders: yes / no

- Do you have an indwelling urinary catheter? yes / no

- Do you have urgency or urinary incontinence? yes / no If yes, how often?:

- Do you get up to urinate at night? yes / no If yes, how many times?

- Do you have difficulty starting urination? yes / no

- Do you perform intermittent drilling? yes / no

3. Sleep disorder: yes / no

- Do you have trouble to move in bed? yes / no

- Do your legs move at night? yes / no

- Have you ever done a sleep study or polysomnography? yes / no - Do you take any sleep pills? yes / no If yes, which one? - Do you wake up tired / fatigued? yes / no - Do you have fatigue during the day? yes / no
4. Do you find that spasticity limits the distance you can walk? yes / no - Do you do any kind of physical activity and/or rehabilitation? yes / no If yes, which? - How much time do you spend exercising in a week? - Do you think it is beneficial for spasticity? yes / no
5. Do you think that spasticity affects your mood? yes / no
Do you think it is helpful to discuss the symptoms of spasticity with the nurse? yes / no If it hadn't been asked, would you have mentioned it? yes / no

Table 2. Demographic and clinical data of participants.

	MS participants (n=368)
Age in years, mean (SD)	45.8 (10.9)
Sex, woman, n (%)	244 (66.3)
MS type, n (%)[1]	
Relapsing-remitting	295 (81)
Secondary progressing	37 (10.2)
Primary progressing	32 (8.8)
Disease duration in years, mean (SD)	8.8 (9)
EDSS, median (range)	2.5 (0-8.5)
Years of schooling, mean (SD)	16 (4.3)
Employment status, active, n (%)	168 (45.7)
Marital status, n (%)	

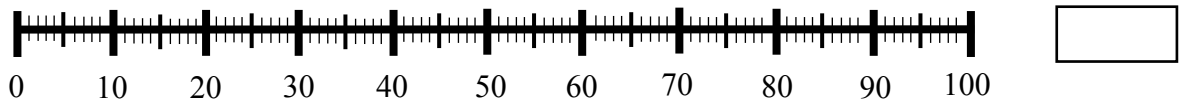
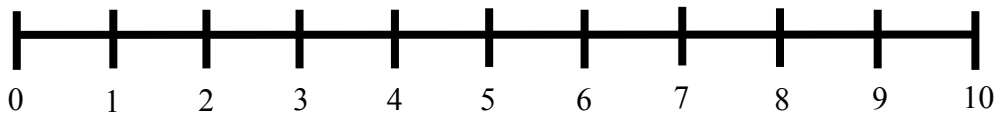
Single	111 (30.1)
Married	224 (60.9)
Divorced/Widowed	33 (9)
Disease modifying therapy, n (%)	
First line	167 (45.4)
Second line	132 (35.9)
Third line	22 (6)
Clinical trial	2 (0.5)
No treatment	45 (12.2)

Abbreviations: MS= multiple sclerosis; EDSS = Expanded Disability Status Scale; SD= standard deviation; Disease modifying was classified as first line (interferon beta, glatiramer acetate, teriflunomide and dimethyl fumarate), second line (natalizumab, fingolimod, cladribine, ocrelizumab and rituximab) and third line (alemtuzumab and mitoxantrone).

Figure legend.

Figure 1. Flow diagram of the study selection process (figure 1A) and a bar graph listing the limiting symptoms of the activities of daily living and their frequency in absolute number and percentage (figure 1B). Abbreviations: ADL= activities of daily living

Table 1. The structured interview for assessing limitations in activities of daily living in people with MS

Demographic data: Age, sex, marital status, current employment and educational level **Multiple sclerosis (MS) data:** MS type / MS diagnosis / EDSS score / Current disease modifying treatment
Is there any limiting symptom related to MS that effect your activities of daily living? yes/no **If yes:** Which one? What is the limitation?
We would like to know how good or bad is your health perception today. This scale goes from 0 to 100. One hundred represents the best health perception that you could imagine, and 0 the worst. Select with an X where you believe it suits you and write the number inside the box 
Do you know what is spasticity? yes/no **Do you think you suffer from spasticity?** yes/no **Has your doctor ever tell you to have spasticity?** yes/no When did spasticity and related symptoms start? Spasticity numeric rating scale (0-10): 

Are you currently receiving treatment? Which?

- Start date of the first treatment:

- Number of previously used treatments: 0 1 2 > 2

- How satisfied do you feel about treatment of spasticity? (0-10):

Do you have any of the following symptoms?

1. Feeling of stiffness (eg walking / resting), muscle cramps and/or spasms: yes / no

If yes, rate the frequency and pain from 0 to 10:

2. Urinary disorders: yes / no

- Do you have an indwelling urinary catheter? yes / no

- Do you have urgency or urinary incontinence? yes / no If yes, how often?:

- Do you get up to urinate at night? yes / no If yes, how many times?

- Do you have difficulty starting urination? yes / no

- Do you perform intermittent drilling? yes / no

3. Sleep disorder: yes / no

- Do you have trouble to move in bed? yes / no

- Do your legs move at night? yes / no

- Have you ever done a sleep study or polysomnography? yes / no

- Do you take any sleep pills? yes / no If yes, which one?

- Do you wake up tired / fatigued? yes / no

- Do you have fatigue during the day? yes / no

4. Do you find that spasticity limits the distance you can walk? yes / no

- Do you do any kind of physical activity and/or rehabilitation? yes / no If yes, which?

- How much time do you spend exercising in a week?

- Do you think it is beneficial for spasticity? yes / no

5. Do you think that spasticity affects your mood? yes / no

Do you think it is helpful to discuss the symptoms of spasticity with the nurse? yes / no

If it hadn't been asked, would you have mentioned it? yes / no

Table 2. Demographic and clinical data of participants.

	MS participants (n=368)
Age in years, mean (SD)	45.8 (10.9)
Sex, woman, n (%)	244 (66.3)
MS type, n (%)[1]	
Relapsing-remitting	295 (81)
Secondary progressing	37 (10.2)
Primary progressing	32 (8.8)
Disease duration in years, mean (SD)	8.8 (9)
EDSS, median (range)	2.5 (0-8.5)
Years of schooling, mean (SD)	16 (4.3)
Employment status, active, n (%)	168 (45.7)
Marital status, n (%)	
Single	111 (30.1)
Married	224 (60.9)
Divorced/Widowed	33 (9)
Disease modifying therapy, n	

(%)	167 (45.4)
First line	132 (35.9)
Second line	22 (6)
Third line	2 (0.5)
Clinical trial	45 (12.2)
No treatment	

Abbreviations: MS= multiple sclerosis; EDSS = Expanded Disability Status Scale; SD= standard deviation; Disease modifying was classified as first line (interferon beta, glatiramer acetate, teriflunomide and dimethyl fumarate), second line (natalizumab, fingolimod, cladribine, ocrelizumab and rituximab) and third line (alemtuzumab and mitoxantrone).

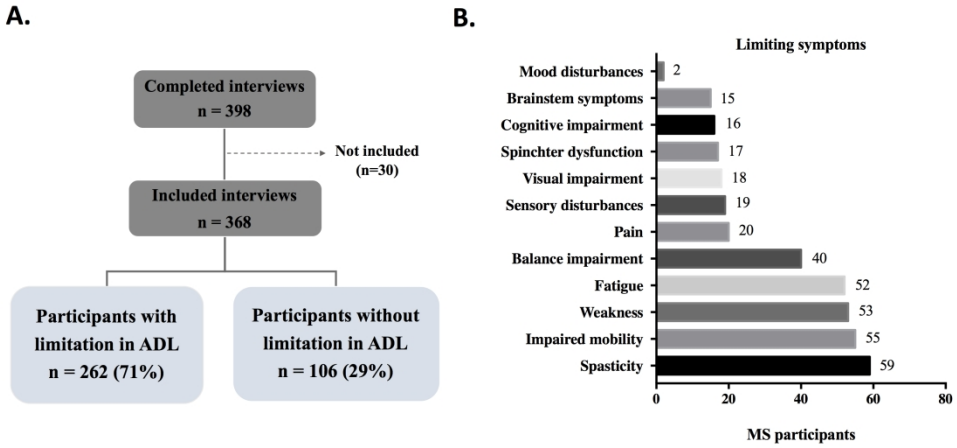


Figure 1. Flow diagram of the study selection process (figure 1A) and a bar graph listing the limiting symptoms of the activities of daily living and their frequency in absolute number and percentage (figure 1B). Abbreviations: ADL= activities of daily living

269x135mm (300 x 300 DPI)

Supplementary file 1. Guidelines for reporting observational studies (STROBE guidelines).

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, line 10
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1 and 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	1, lines 6-9 4, lines 1-5
Methods			
Study design	4	Present key elements of study design early in the paper	1, lines 9-10 4, lines 8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4, lines 11-13
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	No applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, lines 10-25 6, lines 1-17
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6, lines 3-17
Bias	9	Describe any efforts to address potential sources of bias	11, lines 15-23
Study size	10	Explain how the study size was arrived at	5, lines 2-4

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6, lines 3-17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6, lines 3-17
		(*b*) Describe any methods used to examine subgroups and interactions	6, lines 9-11
		(*c*) Explain how missing data were addressed	6, lines 4-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, lines 19-24
		(b) Give reasons for non-participation at each stage	6, lines 19-24
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7, lines 3-8
		(b) Indicate number of participants with missing data for each variable of interest	No applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7, lines 10-15
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(*b*) Report category boundaries when continuous variables were categorized	

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	9, lines 21-22 10, lines 1-2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11, lines 15-23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, lines 1-3
Generalisability	21	Discuss the generalisability (external validity) of the study results	11, lines 9-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12, lines 4-6