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Brief Report

Detecting disability using self-reported and clinical assessments in early-stage relapsing-remitting multiple sclerosis: Looking for a complementary approach

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Abstract

Disability accrual is mainly driven by progression independent of relapse activity, which is present even in early stages of relapsing-remitting multiple sclerosis (RRMS) and sometimes overlooked. This multicenter, non-interventional study evaluated whether patient-reported outcomes measures (PROMs) could capture disability in 189 early-stage RRMS patients (mean age: 36.1 ± 9.4 years, 71.4% female, mean disease duration: 1.4 ± 0.8 years, median EDSS: 1.0). The 9-Hole Peg Test (9-HPT), NeuroQoL Upper Extremity (NeuroQoL-UE), Timed 25-Foot Walk (T25-FW), Multiple Sclerosis Walking Scale (MSWS-12), Symbol Digit Modalities Test (SDMT), and Perceived Deficits Questionnaire (PDQ-5) were used to assess hand function, gait, and cognition, respectively. These functions were at least mildly affected in this early-stage population, finding significant correlations between PROMs and clinical assessments. PROMs could enable early-stage RRMS patients to communicate their perceived disability in different domains, assisting clinicians in disease monitoring and decision making.

Keywords: Relapsing-remitting multiple sclerosis, patient-reported outcomes, early-stage, disability progression

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Introduction

Irreversible disability accumulation in multiple sclerosis can occur through relapse associated worsening and progression independent of relapse activity, being the latter pointed out as the main contributor even in early stages of relapsing-remitting multiple sclerosis (RRMS), and sometimes underestimated at this point.[1,2] Previous studies have shown that balance, walking endurance, and manual dexterity are impaired in one-third to half of these patients,[3] whereas 25–57% present cognitive decline in first few years after diagnosis.[4] Patient-reported outcome measures (PROMs) could help clinicians when assessing these signs of disability progression.[5] The aim of this study was to evaluate whether PROMs are able to capture disability in early-stage RRMS patients.

Methods

Study design

We conducted a multicenter, non-interventional, cross-sectional study. Eligibility criteria included age ≥18 years, diagnosis of RRMS,[6] disease duration ≤3 years, and Expanded Disability Status Scale

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(EDSS) score between 0 and 5.5. Patients not able to understand or complete the study questionnaires according to physician's criteria, including those who had a relapse close to the study visit or who were not stable on their treatment, were excluded. Patients were consecutively recruited at 21 hospital-based neuroimmunology clinics between November 2020 and March 2021. This study was approved by the investigational review board of Hospital Universitari Arnau de Vilanova (Lleida, Spain). All participants provided written informed consent.

Outcome measures

Neurologists collected patients' sociodemographic and clinical characteristics. The 9-Hole Peg Test (9-HPT),[7] Timed 25-Foot Walk (T25-FW),[8] and Symbol Digit Modalities Test (SDMT)[9] were used by neurologists to assess hand function, gait, and cognition, respectively, whereas the NeuroQoL Upper Extremity (NeuroQoL-UE),[10] Multiple Sclerosis Walking Scale (MSWS-12),[11] and Perceived Deficits Questionnaire (PDQ-5)[12] were the corresponding PROMs completed by patients to assess the same functions (Table 1).

Table 1. Outcome measure definitions, scoring, and ranges.

Outcome	Outcome measures	Definition and scoring	Range
Hand dexterity	9-HPT	The 9-HPT assesses upper extremity function by measuring the time spent in placing and removing nine pegs. A cut-off of >33.3 s determines global hand and upper limb dysfunction[7]	Maximum 300 s
	NeuroQoL-UE	The NeuroQoL-UE assesses patients' ability to carry out activities involving digital (e.g. making a phone call), manual, and reach-related functions (e.g. washing and drying themselves). It is an 8-item form rated from 1 = I cannot do it to 5 = I can do it without difficulty[10]	8–40
Gait	T25-FW	The T25-FW evaluates patients' lower extremity function by walking 25 feet. A cut-off of ≥6 s is associated with a change in occupation due to MS or walking with a cane, whereas a cut-off of ≥8 point is associated with walking with a walker, inability to do instrumental activities of daily living or receiving government aids[8]	Maximum 180 s
	MSWS-12	The MSWS-12 assesses the difficulties experienced by individuals in walking function and quality. Each of 12-items is rated from 1 = not at all to 5 = extremely[11]	12–60, transformed into 0–100
Cognition	SDMT	The SDMT measures patient attention and information processing speed. A cut-off of ≤49 correct substitutions is used to identify participants with cognitive problems[9]	0–110
	PDQ-5	The PDQ-5 is a short 5-item version that assesses cognitive complaints perceived by patients on four subscales (Attention/Concentration, Planning/Organization, Retrospective Memory, and Prospective Memory). Each of the 5 items is rated from 0 = never to 5 = almost always[12]	0–5

9-HPT: 9-Hole Peg Test; MSWS-12: Multiple Sclerosis Walking Scale; NeuroQoL-UE: NeuroQoL Upper Extremity; PDQ-5: Perceived Deficits Questionnaire; SDMT: Symbol Digit Modalities Test; T25-FW: Timed 25-Foot Walk.

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Methodological approach

For the descriptive analysis, categorical variables were described as the total number of available values and relative percentage per subgroup of interest. Continuous variables were described by the number of available values, mean, standard deviation, and median, Q1, Q3, minimum and maximum.

Outcome measures associations were analyzed using Fisher's exact test correlation, Kruskal-Wallis test, and Mann-Whitney U test. Correlations were analyzed categorizing the sample according to cut-off points in each outcome described in Table 1.

Results

A total of 189 patients were included in the study. The mean age was 36.1 years and 71.4% were female. Mean disease duration was 1.4 years and median EDSS score was 1.0. Hand dexterity, gait, and cognition impairment were present in 3.7%, 24.6%, and 43.1% of patients, respectively. Sociodemographic and clinical characteristics are shown in Table 2.

MSWS-12 and T25-FW

Moderate-to-extreme limitation on the MSWS-12 was reported by 24.3%, 17.5%, and 18.5% of patients in running, balance, and endurance abilities, respectively. Of patients, 66.1% reported some impact on

Table 2. Sociodemographic and clinical characteristics of patients.

Variables	$N = 189$
Age, years, mean (SD)	36.1 (9.4)
Gender (female), *n* (%)	135 (71.4)
Years of school, *n* (%)	
>16	143 (75.7)
12–16	34 (18)
6–12	10 (5.3)
Other	2 (1.1)
Living status, *n* (%)	
With a partner/family member	164 (86.8)
Time since diagnosis, years, mean (SD)	1.0 (0.8)
Time since first attack, years, mean (SD)	1.4 (0.8)[a]
Number of relapses since first attack, mean (SD)	1.8 (8.4)
Number of relapses in the last year, mean (SD)	0.9 (1.0)
Number of patients on disease modifying therapy, *n* (%)	132 (69.8)
EDSS score (0–10), median (IQR)	1.0 (0–2.0)
9-HPT score (dominant hand), mean (SD), seconds	20.2 (7.5)[b]
>18 to ≤33 seconds, *n* (%)	116 (62.0)
>33 seconds, *n* (%)	7 (3.7)
T25-FW score, mean (SD), seconds	5.8 (3.6)[c]
≥6 and <8 seconds, *n* (%)	21 (11.5)
≥8 seconds, *n* (%)	24 (13.1)
SDMT score (0–110), mean (SD)	51.7 (14.7)
≤49 correct answers, *n* (%)	81 (43.1)
MSWS-12 global score (0–100), median (IQR)	6.3 (0–22.9)
NeuroQoL-UE global score (8–40), mean (SD)	38.5 (3.7)
<40 global score, *n* (%)	57 (30.2)
PDQ-5 global score (0–5), mean (SD)	5.0 (4.4)
Attention/Concentration, median (IQR)	1 (0–2)
Planning/Organization, median (IQR)	2 (0–3)
Retrospective memory, median (IQR)	0 (0–2)
Prospective memory, median (IQR)	4 (1–8)

9-HPT: 9-Hole Peg Test; EDSS: Expanded Disability Status Scale; IQR: Interquartile Range; MSWS-12: Multiple Sclerosis Walking Scale; NeuroQoL-UE: NeuroQoL Upper Extremity; PDQ-5: Perceived Deficits Questionnaire; SD: Standard deviation; SDMT: Symbol Digit Modalities Scale; T25-FW: Timed 25-Foot Walk.
[a]$n = 188$, [b]$n = 187$, [c]$n = 183$.

Table 3. Relationships between PROMs and clinical assessments ($n = 189$).

T25-FW[a]	<6 seconds ($n = 138$)	≥6 and <8 seconds ($n = 21$)	≥8 seconds ($n = 24$)	p-value*
Total MSWS-12 score (0–100), median (IQR)	6.2 (0.0–16.1)	16.7 (6.2–35–4)	5.2 (0.0–41.1)	0.041

	DH[b], seconds			NDH[c], seconds			
9-HPT	≤18 ($n = 64$)	>18 to ≤33 ($n = 116$)	>33 ($n = 7$)	≤18 ($n = 44$)	>18 to ≤33 ($n = 137$)	>33 ($n = 7$)	p-value[†]
NeuroQoL-UE score <40, n (%)	11 (17.2)	39 (33.6)	6 (85.7)	9 (20.5)	42 (30.7)	6 (85.7)	DH: <0.001 NDH: 0.003
NeuroQoL-UE score = 40, n (%)	53 (82.8)	77 (66.4)	1 (14.3)	35 (79.5)	95 (69.3)	1 (14.3)	

SDMT	>49 successes ($n = 107$)	≤49 successes ($n = 81$)	p-value**
PDQ-5 Attention/Concentration score, mean ± SD	0.95 ± 1.09	1.36 ± 1.32	0.04
PDQ-5 Planning/Organization score, mean ± SD	1.56 ± 1.55	2.22 ± 2.01	0.03
PDQ-5 Retrospective Memory score, mean ± SD	0.83 ± 0.99	0.89 ± 1.16	0.996
PDQ-5 Prospective Memory score, mean ± SD	0.95 ± 0.97	1.37 ± 1.21	0.022
PDQ-5 Global score, mean ± SD	4.30 ± 3.78	5.84 ± 4.98	0.053

9-HPT: 9-Hole Peg Test DH: Dominant hand; IQR: interquartile range; MSWS-12: Multiple Sclerosis Walking Scale; NDH: Non-Dominant Hand; NeuroQoL-UE: NeuroQoL Upper Extremity; PDQ-5: Perceived Deficits Questionnaire; PROMs: Patient Reported Outcome Measurements; SD: standard deviation; SDMT: Symbol Digit Modalities Test; T25-FW: Timed 25-Foot Walk.

[a]$n = 183$, [b]$n = 187$, [c]$n = 188$.

*Kruskal-Wallis test; [†]Fisher's exact test; **Mann-Whitney U-test. A cut-off of <40 is used to categorize patients with some limitation in at least one of the activities listed in the NeuroQoL-UE questionnaire versus patients with no limitation.

walking ability. All individual item scores but one were significantly correlated with T25-FW score, the need for support when walking indoors being non-significant ($p = 0.054$). Total MSWS-12 score was significantly correlated with categorized T25-FW score (Table 3).

NeuroQoL-UE and 9-HPT

Writing with a pen/pencil and picking up coins from a table top were the tasks with the highest proportion of patients (8.5%) reporting some or a lot of difficulty in performance. A proportion of 30.2% of patients had some limitation in at least one of the questionnaire activities. Each individual NeuroQoL-UE item had a significant correlation with dominant and non-dominant 9-HPT categorized scores ($p < 0.001$). Total NeuroQoL-UE score was significantly correlated with 9-HPT dominant and non-dominant hands (Table 3).

PDQ-5 and SDMT

Of patients, 82% reported problems in at least one dimension of the PDQ-5 and Planning/Organization was the most affected domain. Attention, Planning/Organization, and Prospective memory domains were significantly correlated with SDMT categorized score (Table 3).

Discussion

Disability accrual in MS is present from the start and can be independent of relapses. Identifying it is important to establish rehabilitation programs and to adapt treatment regimens to achieve long-term outcomes. In our study, gait, hand dexterity, and cognition were functions frequently affected in early-stage RRMS. Short and easy-to-complete PROMs can be used as a complementary strategy to clinical assessments.

Previous studies have found significant associations between MSWS-12 and balance impairment, fatigue and increased gait asymmetry, and instability in early-stage RRMS patients, supporting its use in this population.[13] We found significant correlations between categorized T25-FW and all MSWS-12 dimensions but support needed indoors, probably because of the population's early-stage nature and low impairment reported. However, a greater percentage of patients reported some impact on their walking ability than that reflected by the T25-FW when using the cut-off point of 6 s, supporting the MSWS-12 as a complementary tool.

The 9-HPT has previously shown significant correlations with NeuroQoL-UE total score.[10] Not only total score but individual items showed significant correlations for both dominant and non-dominant hands in this study in early-stage RRMS, providing additional evidence.

Contrary to our results, previous investigators have been unable to find a correlation between total score or individual dimensions of the PDQ and SDMT.[12] However, the PDQ used was the 20-item version and participants were older, with longer time since diagnosis, and different forms of MS.

To our knowledge, this is the first study assessing simultaneous correlations between PROMs and clinical assessments regarding gait, hand dexterity, and cognition in patients with short disease duration and low physical disability, and it is the first study in demonstrating significant correlations between the PDQ-5 and SDMT. Nonetheless, several limitations should be mentioned, as we did not correct the SDMT scores according to age and education normative data, we did not assess the influence of symptoms (fatigue, depression, or anxiety) on outcomes assessed, and the small sample size and the cross-sectional design did not allow us to assess changes or causal relationships in correlations between PROMs and clinical assessments over time.

In conclusion, disability accrual is already present in early-stage RRMS patients, affecting their hand dexterity, gait, and cognition. The NeuroQoL-UE, MSWS-12, and PDQ-5 are useful tools to screen for specific difficulties or quickly assess whether a patient needs a referral for more extensive testing, carry out neuropsychological batteries, or use portable widgets to monitor exact domains or movements. This approach could assist clinicians in disease monitoring and decision making, and would open the possibility of recommending early physical and cognitive rehabilitation.

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