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ORIGINAL COMMUNICATION

Walking function in clinical monitoring of multiple sclerosis by telemedicine

Núria Sola-Valls[1] · Yolanda Blanco[1] · Maria Sepúlveda[1] · Sara Llufriu[1] · Elena H. Martínez-Lapiscina[1] · Delon La Puma[1] · Francesc Graus[1] · Pablo Villoslada[1] · Albert Saiz[1]

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Abstract Walking limitation is a key component of disability in patients with multiple sclerosis (MS), but the information on daily walking activity and disability over time is limited. To determine, (1) the agreement between the standard measurements of MS-related disability [expanded disability status scale (EDSS), functional systems (FS) and ambulation index (AI)] obtained by conventional and remote evaluation using a multimedia platform; (2) the usefulness of monitoring 6-min walk test (6MWT) and average daily walking activity (aDWA) to better characterize patients disability. Twenty-five patients (EDSS score 1.0–6.5) were evaluated every 3 months for the first year, and aDWA repeated at year 2. Remote visits included the recording of a video with self-performed neurological examination and specific multimedia questionnaires. aDWA was measured by a triaxial accelerometer. All but two patients completed the study. Modest agreement between conventional and multimedia EDSS was found for EDSS $\leq$ 4.0 (kappa = 0.2) and good for EDSS $\geq$ 4.5 (kappa = 0.6). For the overall sample, pyramidal, cerebellar and brainstem FS showed the greatest agreement (kappa = 0.7). SR-AI showed a modest agreement for EDSS $\leq$ 4.0 and good for EDSS $\geq$ 4.5 (kappa = 0.3 and 0.6, respectively). There was a strong correlation between conventional and 6MWT measured by accelerometer ($r = 0.76$). The aDWA correlated strongly with the EDSS ($r = -0.86$) and a cut-off point of 3279.3 steps/day discriminated patients with ambulatory impairment. There was a significant decline in aDWA over 2 years in patients with ambulatory impairment that were not observed by standard measurements of disability. MS clinical monitoring by telemedicine is feasible, but the observed lower agreement in less disabled patients emphasizes the need to optimize the assessment methodology. Accelerometers capture changes that may indicate deterioration over time.

Keywords Multiple sclerosis · Telemedicine · Disability progression · Accelerometer · Daily walking activity

Introduction

Telemedicine, described as the "use of communication technologies to assist in the diagnosis and treatment of medical conditions through the transmission of data between two different physical places", offers the potential of improving accessibility to health services [1] but reports on using this potentially promising technology with reliable markers of disability and walking activity are limited. Presently, the expanded disability status scale (EDSS) is the standard measurement of disability and disease progression in multiple sclerosis (MS), but it has several limitations. At the lower end of the scale (EDSS score $\leq$ 4.0), the score is influenced by signs detected in the neurological examination, while higher EDSS scores (EDSS $\geq$ 4.5) is mainly based on walking ability [2–4]. In addition, the EDSS is less responsive to changes in patients with greater disability [3, 4]. Gait impairment is a frequent finding over the course of MS, but there appears to be a reduction of speed and stride length during walking in people with mild MS compared with age- and sex-matched control subjects [5, 6]. The usual tools to measure walking function are short lasting standard

✉ Yolanda Blanco
yblanco@clinic.ub.es

[1] Service of Neurology, Hospital Clínic and Institut dÍnvestigació Biomèdica August Pi i Sunyer (IDIBAPS), Center of Neuroimmunology, Universitat de Barcelona, Villarroel 170, 08036 Barcelona, Spain

tests such as the timed 25-foot walk (T25FW) and the longer 2 or 6-min walk test (2MWT or 6MWT). Recently, accelerometers have been introduced to measure continuous ambulation in real life conditions [7]. The aims of this longitudinal pilot study were: (1) to examine the feasibility of using a multimedia platform and determine the reliability of the obtained EDSS (multimedia EDSS) in comparison with the conventional EDSS (standard physical neurological examination), and (2) to explore the usefulness of monitoring continuous ambulation (daily walking activity measured by an accelerometer) to better characterize the patient's disability status and its potential use for detecting disease progression over time in a cohort of MS patients.

Methods

Patients

Twenty-five consecutive MS patients were prospectively selected from the MS Unit of the Hospital Clinic of Barcelona. The inclusion criteria were: (1) clinically definite MS according to 2010 McDonald criteria [8]; (2) relapsing-remitting or secondary progressive forms; (3) EDSS score between 1.0 and 6.5; and (4) availability of a home computer with internet connection.

Study schedule and procedures

This longitudinal study included six visits, one every 3 months (month 0, 3, 6, 9 and 12) for 1 year, and one additional visit after 2 years of follow-up (Fig. 1). The first year, each visit included a double evaluation, first at the Hospital (conventional visit) and the following day at home (remote visit). Conventional and remote visits were evaluated by two independent and blinded raters. The conventional visit included a neurological examination, recording of the EDSS [2], the multiple sclerosis functional composite (MSFC) [9], and the performance of the 6MWT [10]. The following day after each conventional visit, patients were remotely evaluated by a multimedia system: a health management platform created by Linkcare Health

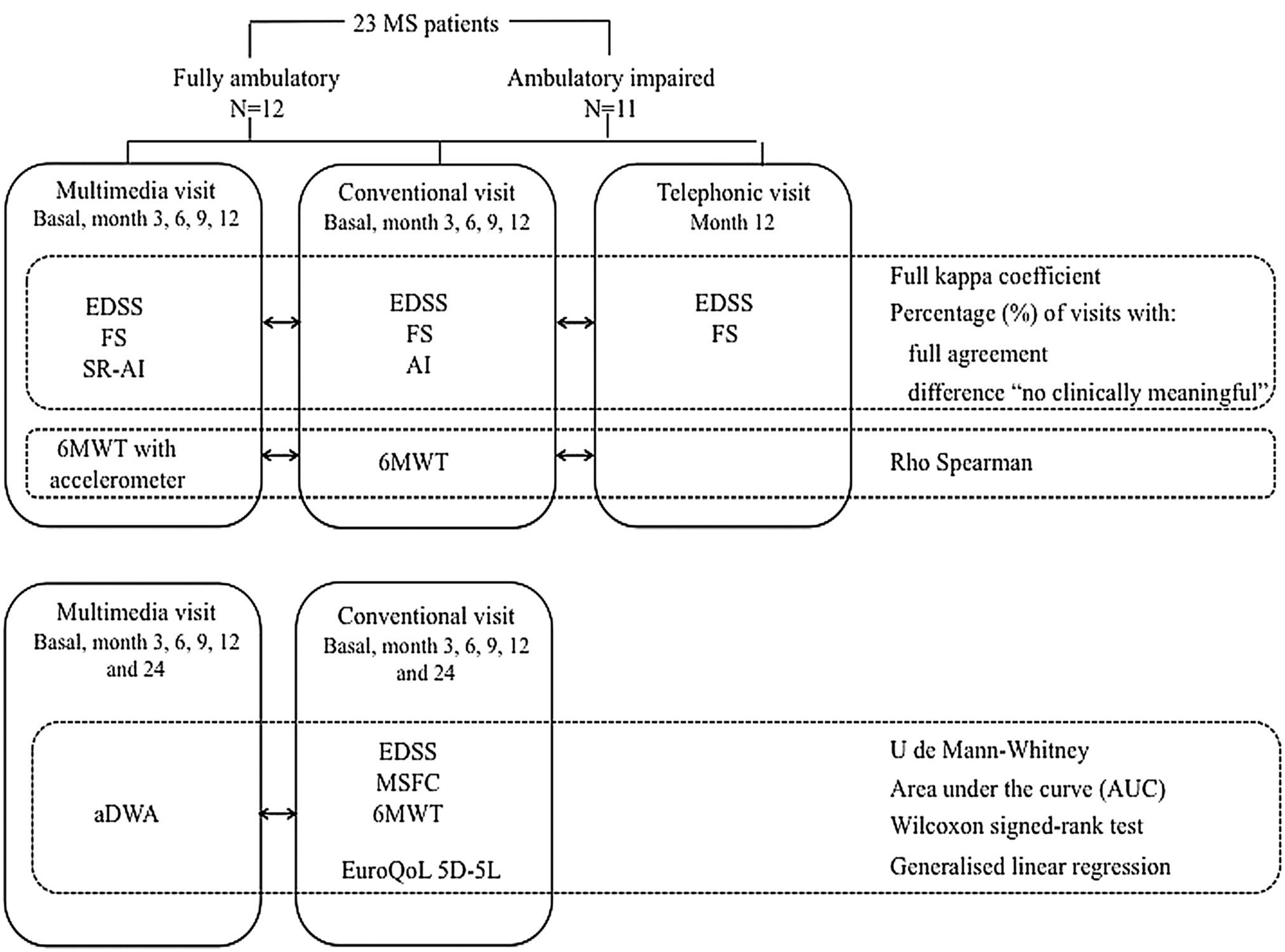

Fig. 1 Study procedures and assessments. *EDSS* expanded disability status scale, *FS* functional systems, *AI* ambulation index, *SR-AI* self-reported ambulation index, *MSFC* multiple sclerosis functional composite, *6MWT* 6-min walk test, *aDWA* average daily walking activity

Services SL (http://www.linkcare.es). This remote visit included recording a video of a self-performed neurological examination (patients were previously trained) to evaluate pyramidal, cerebellar and brainstem functional systems (FS); visual FS was measured by an electronic Snellen eye chart; sensory, bowel and bladder FS were evaluated by a set of electronic questions [11] and cognitive FS by the questionnaire of the multiple sclerosis quality of life (MSQoL) inventory [12]. Walking distance was graded from 0 to 12 according to ambulation index (AI) score by neurostatus definitions [using the measured distance in the conventional visit, and the estimated by the patient in the self-reported AI (SR-AI)] [11]. Every 6 months, this remote visit also included an evaluation of fatigue and depression [12]; fatigue was determined by the modified fatigue impact scale (MFIS), which scores range from 0 to 84, with higher scores indicating a greater impact of fatigue on a patient's activities, and depression was determined by the mental health inventory (MHI) which scores range from 0 to 100, with higher scores indicating better mental health. At the end of the first year, the assessment of the EDSS by a telephone questionnaire [13] and the quality of life by the EuroQoL 5D-5L [14] instrument were administered to all patients. The additional visit at year 2 included the conventional visit with the recording of the EDSS, the MSFC and the performance of the 6MWT (Fig. 1).

Remote walking assessment

The following day after each conventional visit, patients performed the 6MWT test at home with a portable triaxial accelerometer (Actigraph GT3X) and subsequently wore the accelerometer for a period of 7 consecutive days. The accelerometer was worn on an elastic belt around the non-dominant hip determined by the Edinburgh handedness inventory [15]. Patients were asked to wear it the entire day, except while sleeping, and were instructed to do their usual routine. To ensure the consistency of accelerometer data, we designated a valid measurement as $\geq$3 days of accelerometer activity with $\geq$10 h without any period of $\geq$60 min of no accelerometer data (continuous zeros). Average daily walking activity (aDWA) was measured in steps during the day (steps/day) because this parameter has shown the highest correlation between the EDSS and standardized walking tests: T25FW (seconds) and 6MWT (meters) [16].

Statistical analysis

In this pilot study, we calculated a sample size of 25 participants according to previous research that suggest that it should be 10 % of the sample projected for the larger study in the field with an α and β error of 0.05 and 0.80, respectively, and a small effect size (0.10). Full agreements measured by kappa coefficients and values of Pearson's correlation coefficients were rated as previously reported [17, 18]. Moreover, we evaluated the percentage of visits with full agreement, and the percentage of visits that had a change of the EDSS lower than what was considered as clinically meaningful in clinical trials (a change of at least 1.0 point at EDSS level $\leq$ 5.0 or at least 0.5 point at EDSS level $\geq$ 5.5) [19]. Disease progression was defined as: a change of at least 1.0 point at EDSS level $\leq$ 5.0 or at least 0.5 point at EDSS level $\geq$ 5.5 [19] and/or a worsening from baseline on scores of at least one MSFC component by 20 % [20]. Patients were grouped by their EDSS score in fully ambulatory patients (EDSS $\leq$ 4.0) and patients with ambulatory impairment (EDSS $\geq$ 4.5). Differences across ambulation subgroups were performed by Mann–Whitney *U* test. Accuracy of the potential predictive value of an accelerometer to detect patients with EDSS $\geq$ 4.5 was analyzed by the area under the curve (AUC). Generalized linear regression analysis was conducted by regressing aDWA and EDSS, and included age, body mass index, fatigue and mood score as confounding variables. Longitudinal data was analyzed by Wilcoxon signed-rank test for paired nonparametric comparisons. All p values were two tailed and they were considered significant at $p \leq 0.05$. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA) software.

Results

Patients' characteristics and feasibility of remote monitoring

Twenty-three of the 25 (92 %) patients completed the study. One patient withdrew from the study after the first visit because she was unable to attend the physical visits, and the second after having a heart attack. Demographic and clinical characteristics of the 23 patients who completed the study are shown in Table 1. Eleven of the 23 (48 %) patients had an EDSS score $\geq$ 4.5. Nearly half of the patients (42 %) had minor technical problems during the study (i.e., problems in sending the video or answering the questionnaires) but these problems were solved easily. Nineteen (85 %) participants reported telemedicine monitoring as a positive experience and eight (35 %) found it highly suitable.

Agreement between conventional and remote measurements

Overall full agreement between conventional and multimedia EDSS measures was modest for fully ambulatory patients [EDSS $\leq$ 4.0; kappa = 0.20, 95 % confidence interval (CI) 0.1–0.3, $p < 0.01$] and good for patients with ambulatory

Table 1 Demographic and clinical characteristics of the study sample

	MS patients ($N = 23$)
Sex, female:male	12:11
Age, years; mean (SD)	46.7 (10.0)
MS type, RR:SP	15:8
BMI, kg/m^2; mean (SD)	24.4 (4.0)
Smoking (%)	21.7
MFIS score; mean (SD)	55.3 (17.1)
MHI score; mean (SD)	57 (8.2)
Disease duration, years; mean (SD)	14.2 (9.9)
EDSS; median (range)	3.5 (1.5–6.5)
ARR; mean (SD)	0.5 (0.4)
MSSS; mean (SD)	4.8 (8.9)
Time to EDSS 4.0, years, mean (SD)	9.6 (3.6)
Time to progressive phase, years; mean (SD)	14.1 (13.0)

MS multiple sclerosis, *SD* standard deviation, *RR* relapsing-remitting, *SP* secondary progressive, *BMI* body mass index, *MFIS* modified fatigue impact scale, *MHI* mental health inventory, *EDSS* expanded disability status scale, *ARR* annualized relapse rate, *MSSS* multiple sclerosis severity score

impairment (EDSS ≥ 4.5; kappa = 0.60, 95 % CI 0.4–0.8, $p < 0.01$) (Table 2). Conventional and multimedia agreement in FS was good for pyramidal (kappa = 0.70, 95 % CI 0.6–0.8, $p < 0.01$), cerebellar (kappa = 0.71, 95 % CI 0.6–0.8, $p < 0.01$) and brainstem (kappa = 0.70, 95 % CI 0.6–0.8, $p < 0.01$), and low to moderate for the other FS (Fig. 2). Full agreement between both EDSS measures was observed in 45 % of visits, and increased to 82 % when the change in the EDSS was not considered clinically meaningful (a change of 0.5 points in patients with EDSS level ≤ 5.0). Multimedia EDSS showed better agreement than telephonic EDSS when compared with conventional EDSS measures. Full agreement between conventional and telephonic EDSS was poor for fully ambulatory patients (kappa = 0.05, 95 % CI −0.1 to 0.3, $p = 0.6$) and moderate for patients with ambulatory impairment (kappa = 0.50, 95 % CI 0.1–0.9, $p = 0.25$) (Table 2). Full agreement was observed in 36 % of the visits, and increased to 72 % when the change in the EDSS was not considered clinically meaningful. The agreement between conventional and telephonic FS ranged from poor to modest, but the kappa values were always lower than the observed between the conventional and multimedia FS (data not shown). A moderate agreement was observed between the conventional and SR-AI for the entire sample (kappa = 0.52, 95 % CI 0.3–0.7, $p < 0.01$) but full agreement was observed in 68.2 % of visits; patients with ambulatory impairment showed good agreement (kappa = 0.60, 95 % CI 0.2–1, $p < 0.01$) in contrast with fully ambulatory patients (kappa = 0.30, 95 % CI −0.2 to 0.6, $p = 0.2$) (Table 2).

Remote monitoring of continuous ambulation by accelerometer

The 6MWT evaluated by accelerometer correlated strongly with conventional 6MWT ($r = 0.76$, $p < 0.01$). A robust correlation was also found between aDWA and the EDSS score ($r = -0.86$, $p < 0.01$). In the generalized linear regression model, disability status (EDSS score) was the single significant predictor that accounted for 76 % of the variance in aDWA (adjusted $R^2 = 0.76$, $p < 0.01$). When the model was applied to patients with an EDSS score ≥ 4.5, the result remained similar ($R^2 = 0.77$, $p < 0.01$), but it decreased to 22 % in patients with an EDSS score ≤ 4.0 ($R^2 = 0.22$, $p = 0.21$). The mean ± SD aDWA of the total sample was 5597.3 ± 3751.7 steps/day. There were significant differences between fully ambulatory patients (7283.4 ± 3141.6 steps/day) and those with ambulatory impairment (1550.9 ± 943.1 steps/day) ($p < 0.01$), and these differences were maintained throughout the study (Fig. 3). A cut-off point of 3279.3 steps/day was able to discriminate patients with ambulatory impairment from fully ambulatory patients with a high sensitivity (0.9), specificity (1.0) and accuracy (AUC = 0.99, 95 % CI 0.97–1.0, $p < 0.01$). Using this cut-off point, a significant difference in the EuroQoL 5D-5L index value was observed between fully ambulatory patients and those with ambulatory impairment (0.8 vs. 0.6, respectively, $p < 0.01$). The linear regression equation indicated that every 1-point increase in the EDSS score yielded a reduction of 1198.2 steps/day (95 % CI 2079–317.4, $p = 0.09$) in fully ambulatory patients, and a reduction of 1340.4 steps/day (95 % CI 2134.3–546.5, $p < 0.02$) in patients with ambulatory impairment.

Longitudinal walking assessment

After 2 years of follow-up, four patients (17.4 %) had a relapse but no progression of the disease was observed in any patient included in the study. Indeed, no evidence of disability progression was observed by the EDSS score (mean difference = −0.04, $p = 0.65$) or the MSFC *z*-score (mean difference = 0.1, $p = 0.14$) in the overall sample. Focusing on walking assessments, we observed a significant decline in aDWA over time (mean difference = 1717.7 steps/day, $p = 0.01$), mainly explained by a significant decrease in patients with ambulatory impairment (mean difference = 1279 steps/day, $p = 0.02$), and a trend in fully ambulatory patients (mean difference = −2119.9 steps/day, $p = 0.08$). By contrast, fully ambulatory patients showed a mild improvement in the 6MWT (mean difference = 47.2 m, $p = 0.04$), whereas the changes were not significant in patients with

Table 2 Inter-rater agreement between conventional and remote measurements

		Total sample	Fully ambulatory (EDSS ≤ 4.0)	Ambulatory impaired (EDSS ≥ 4.5)
Conventional vs. multimedia EDSS	Kappa coefficient (95 % CI)[a]	0.4 (0.3–0.5)	0.2 (0.1–0.3)	0.6 (0.4–0.8)
	Percentage (%) of visits with:			
	Full agreement[b]	44.8	33.8	44.8
	Difference "no clinically meaningful"[c]	81.9	81.1	86.7
Conventional vs. telephonic EDSS	Kappa coefficient (95 % CI)[a]	0.3 (0.1–0.5)	0.05 (−0.1 to 0.3)	0.5 (0.1–0.9)
	Percentage (%) of visits with:			
	Full agreement[b]	36.4	20	62.5
	Difference "no clinically meaningful"[c]	72.2	73.3	75
Self-reported ambulation score vs. measured at hospital	Kappa coefficient (95 % CI)[a]	0.5 (0.3–0.7)	0.3 (−0.2 to 0.6)	0.6 (0.2–1)
	Percentage (%) of visits with:			
	Full agreement[b]	68.2	73.3	62.5

EDSS expanded disability status scale, *CI* confidence interval

[a] Kappa coefficient (95 % CI) refers to a pooled kappa of full agreement considering all visits

[b] Full agreement refers to the number of visits with exact result between conventional and remote measurement

[c] Difference "no clinically meaningful" represents a change of 0.5 points in patients with EDSS level ≤ 5.0

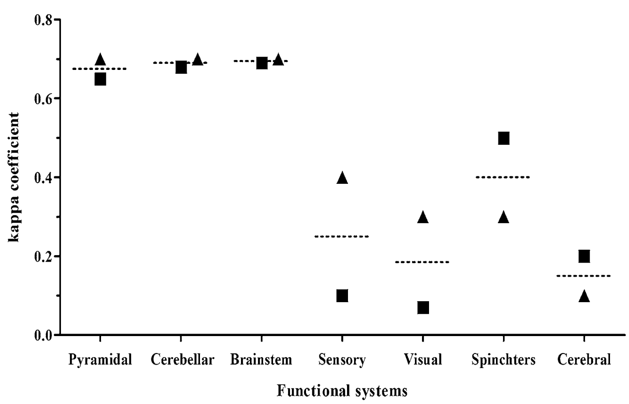

Fig. 2 Full agreement on functional systems of the EDSS between conventional and multimedia measurements. Kappa coefficient was measured according to ambulation subgroups: fully ambulatory patients (■) and patients with ambulatory impairment (▲). *EDSS* expanded disability status scale

ambulatory impairment. Regarding T25FW, no significant change was observed in any group (Table 3).

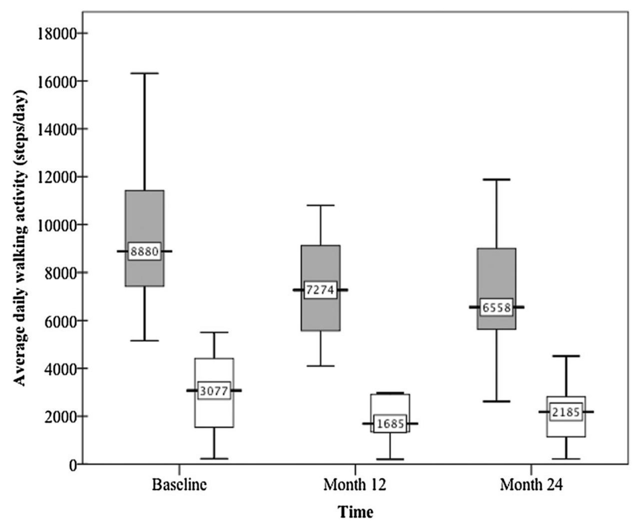

Fig. 3 *Box-plot* of average daily walking activity in ambulation subgroups during the study (*box* 25–75 % percentile range; *central horizontal bar* mean; *whiskers* from minimum to maximum). Average daily walking activity from fully ambulatory patients and patients with ambulatory impairment are plotted in *dark grey* and *white*, respectively

Discussion

This study provides several findings that may be relevant at the time of adopting telemedicine as a tool for clinical monitoring or a therapeutic intervention in MS: (1) the implementation of a program by telemedicine is feasible; (2) good agreement between conventional and remote EDSS is only found in more disabled patients (EDSS score ≥ 4.5); (3) pyramidal, cerebellar and brainstem FS are the more reliable measures of impairment regardless of the degree of disability; (4) SR-AI shows modest agreement for fully ambulatory patients (EDSS score ≤ 4.0); (5) strong correlation is found between conventional 6MWT and the one measured by accelerometer; (6) aDWA correlates strongly with the EDSS score, and can discriminate patients with or without ambulatory impairment; and (7) aDWA can detect changes that are not observed by the standard measurements of disability over time. Taking into account the low reproducibility of the EDSS, especially at the lower end of the scale [3, 4], the finding of a modest

Table 3 Changes in walking measures at 2 years from baseline

		Total sample	p	Fully ambulatory (EDSS ≤ 4.0)	p	Ambulatory impaired (EDSS ≥ 4.5)	p
No. of patients		23		12		11	
aDWA by accelerometer (steps/day)	Mean difference (SD)	−1717.7 (2912.8)	0.01	−2119.9 (3798.4)	0.08	−1279 (1545.4)	0.02
	Mean % of change (SD)	−18.7 (36.8)	na	−19.2 (33.9)	na	−18 (41.3)	na
6MWT (m)	Mean difference (SD)	19.4 (72)	0.21	47.2 (71.3)	0.04	−10.9 (62.3)	0.57
	Mean % of change (SD)	3.1 (22.3)	na	13.1 (20.4)	na	−7.8 (19.6)	na
T25FW (s)	Mean difference (SD)	0.8 (3)	0.23	−0.3 (1)	0.30	2 (4)	0.14
	Mean % of change (SD)	3.6 (23.2)	na	−4.6 (18.1)	na	12.6 (25.5)	na
	Difference of z-score	0.1	0.21	0.1	0.45	0.1	0.31

Mean difference is expressed as 2 years value minus baseline value

EDSS expanded disability status scale, *p* *p* value, *aDWA* average daily walking activity, *6MWT* 6 min walk test, *T25FW* timed 25-foot walk, *SD* standard deviation, *na* no applicable

agreement between conventional and remote EDSS score was not unexpected. In fact, we found similar agreement in the range of inter-rater agreement reported between two physical examiners (kappa of 0.45–0.50) [21–23]. Similarly, we observed a better agreement for those patients more disabled in whom the EDSS score is weighted heavily toward ambulatory disability [24]. However, when we considered that a variation of the EDSS score was not clinically meaningful, the agreement was 82 % regardless of the EDSS score. It is likely that the reduction of the FS scoring variability by the use of a video in the multimedia EDSS assessment has contributed to these results [25, 26]. These results compare favorably with the ones observed by the telephonic interview in terms of better agreement with the EDSS and the FS scores, with a higher percentage of full agreement between conventional and remote assessment. Similar to a previous report with an equivalent kappa coefficient [13], a better reliability was found in patients with higher EDSS scores, indicating that in more disabled patients (EDSS ≥ 4.5), the telephonic interview could be useful when they are unable to attend a visit. The finding of a low agreement between self- and measured-ambulation has been noted previously [27, 28]. In our study, fully ambulatory patients tended to underestimate their walking distances (30 %), whereas in patients with ambulatory impairment, the frequency of under- or over estimation was more variable (12 and 25 %, respectively). This information is not only important at the time of scoring the EDSS but also when interpreting disease progression. Thus, in more disabled patients, a full agreement was only seen in 63 % of the visits, reinforcing the importance of including objective measures of ambulation in clinical monitoring by telemedicine.

In the last decade, accelerometer-based technology has been evaluated for objectively monitoring the total amount of daily activity as a clinical mobility measure of MS patients under real-world conditions [29]. In this sense, we found that the 6MWT, a reliable and valid tool for measuring walking ability, can be monitored remotely by using an accelerometer ($r = 0.76$). Moreover, the strong correlation between aDWA and the EDSS ($r = -0.86$) indicates a commonality between these two measures. Using a cut-off point of 3279.3 steps/day, we were able to identify patients with walking impairment with a high sensitivity and specificity, and these patients showed lower quality of life scores. Although in the whole sample we found that disability status (EDSS score) may explain approximately 76 % of the variance of aDWA, this was true for patients with ambulatory impairment but not for fully ambulatory patients, in whom the EDSS only contributed to 23 % of the variability in aDWA [30]. Altogether, these data would suggest that aDWA could be a good measure of disability in more disabled patients, and perhaps more responsive to changes of disability in this subgroup of patients than clinical measures. We detected a significant decline of the aDWA in patients with ambulatory impairment (EDSS ≥ 4.5), which exceed the standard error of accelerometer measurement [31, 32]. Despite the limitation of our small sample size, this is the first study that documents longitudinal changes in aDWA in comparison with other standardized walking tests. Although standard walking tests are reliable for assessing ambulation under controlled conditions, they may not reflect the real-life circumstances involved in walking impairment, and perhaps may overestimate real ambulation and physical activity. Therefore, the inclusion of new, more sensitive instruments to measure walking function may help to better monitor the disease and identify the rate and predictors of change for the design and delivery of behavioral interventions in this population.

In conclusion, MS clinical monitoring by telemedicine is feasible, but carries several limitations such as the lower reliability of the assessment in less disabled patients. Despite the use of a video-recording that seems to improve the agreement for the most valuable functional systems (pyramidal, cerebellar, and brainstem), our results emphasize the need to optimize the assessment methodology. Although the remote evaluation does not substitute a physical visit, the results support the multimedia EDSS assessment as a reliable tool to monitor especially disabled MS patients at distance. Indeed, changes in ambulatory physical parameters recorded by accelerometers can be used as an objective measurement of clinical monitoring and treatment intervention in MS patients. Large-scale prospective studies are needed to validate aDWA as an adequate instrument for detecting MS disability over time.

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Conflicts of interest Núria Sola-Valls, Yolanda Blanco, Maria Sepúlveda, Sara Llufriu, Elena H Martínez-Lapiscina, Delon La Puma and Francesc Graus declare that there is no conflict of interest. Pablo Villoslada has received consultation fees from Roche, Novartis, Neurotech Pharma and is founder and hold stocks of Bionure Farma. Albert Saiz has received compensation for consulting services and speaking from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd and Novartis.

Ethical standards All participants provided their written informed consent prior to their inclusion in the study. This clinical study was approved by the ethical committee of the Hospital Clinic of Barcelona and therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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