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ORIGINAL RESEARCH ARTICLE

Motor and cognitive changes across 2 years: a longitudinal study in early Multiple Sclerosis

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ABSTRACT

Background: Functional disorders appear early in the course of the disease and develop over time, impacting participation and quality of life. However, little is known about functional deterioration assessed by clinical and instrumented tools in longitudinal studies.

Methods: We included 63 PwMS with Expanded Disability Status Scale (EDSS) ≤2.5 points, disease duration ≤5 years, and age (Mean ± Standard Deviation) 38.7 ± 10.7 years. Participants were assessed at baseline and after 2 years with clinical and instrumented evaluations. Data on disability and functional disorders were collected using EDSS, Six-Minute Walk Test (6MWT), Multiple Sclerosis Walking Scale-12 (MSWS-12), Fatigue Severity Scale (FSS), and Symbol-digit modality test (SDMT), while instrumented data measuring complexity and intensity of balance disorders and gait symmetry-regularity-instability were extracted from wearable devices.

Results: Clinical scales (EDSS, 6MWT, FSS, MSWS-12, and SDMT) did not show a statistically significant deterioration when baseline and 2-year follow-up were compared: EDSS (Median and min-max) from 2 (0-2.5) to 1.5 (0-4.5)points, 6MWT from 566.2 ± 80.4 to 573.9 ± 94.7m, FSS from 2.89 (0.89-7) to 2.67(1-7)points, MSWS-12 from 25 (20-65) to 25 (20-78.3) points, and SDMT from 55.34 ± 14.7 to 61.4 ± 15.5 points. We observed similar results in instrumented variables: complexity from −0.15 ± 1.06 to −0.38 ± 1.08 [au], intensity from 0.00 ± 0.69 to −0.17 ± 0.78 [au], gait regularity from 0.87 ± 0.07 to 0.88 ± 0.08 [au], gait symmetry from 80.24 ± 20.24 to 83.0 ± 8.85 [au], and gait instability from 0.67 ± 0.11 to 0.70 ± 0.13 [au].

Conclusion: We hypothesized that subtle functional deteriorations would be detectable over two years. However, our data showed a functional stability of the disease at follow-up. This held even when an instrumented assessment was added to assess subtle functional disorders.

Keywords: Assessment, Functional disorders, Multiple sclerosis, Rehabilitation, Wearable sensors

What is already known about the topic:

- *Evidence has shown that even participants with EDSS ≤ 2.5 present functional deficits when assessed with specific functional tests.*

What does the study add:

- *Our study is the first longitudinal multicenter study that aims to provide a comprehensive picture of all the functional domains using objective, subjective, and instrumented tools to describe changes over time.*

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Background

Functional impairments in early Multiple Sclerosis

Multiple Sclerosis (MS) is a disabling autoimmune disease of the central nervous system, showing a large heterogeneity in its clinical presentation and course. Among functional disorders, balance disorders, fatigue, and cognitive impairments

are the most common deficits in people with MS (PwMS), significantly impacting activities of daily living (1).

Notably, both static and dynamic balance disorders can emerge early, even in PwMS, who maintain normal walking ability and worsen over time, increasing the risk of falls and loss of independence (2). Fatigue, reported by up to 95% of PwMS, is one of the most debilitating symptoms, often persisting for years, exacerbating during relapses, and sometimes continuing even after recovery. Cognitive impairments frequently affect information processing speed, episodic memory, attention, and executive function, further contributing to disability. Although cognitive deficits have been observed in the early stages of the disease, recent studies suggest that motor impairments may be more prevalent than cognitive impairments in the early stages of MS (3,4).

So far, among clinician-reported outcome measures, the Expanded Disability Status Scale (EDSS) is the most commonly used tool to quantify disability status and disease progression in MS. Although its clinical usefulness has been well-reported over the years, several drawbacks have also been acknowledged (5). In particular, EDSS is not able to detect which specific functional deficits evolve during the course of the disease relative to the others. Compared to EDSS, both performance outcomes and patient-reported outcomes provide a more comprehensive assessment across different functional domains such as balance (e.g., Fullerton Balance Activity Scale), gait (e.g., 6-Minute walk test), upper limb function (e.g., 9-hole peg test), and cognition (Brief International Cognitive Assessment for MS) that are currently used to monitor disease progression from both clinical and patient perspective (6).

The use of technology in Functional Assessment

To overcome the lack of an objective perspective in terms of clinical dependency and measurement accuracy, the use of technology can be a valid solution. Instrumented assessments, particularly wearable inertial measurement units (IMUs) incorporating accelerometers, gyroscopes, and magnetometers, provide a sensitive and cost-effective way to detect subtle, clinically unobservable changes in function. These tools can assess balance and gait without requiring large spaces or extended evaluation times, offering objective measurements that capture small fluctuations in motor function over time (7).

These tools can assess balance and gait without requiring large spaces or extended evaluation times, offering objective measurements that capture subtle impairment not detectable by clinical scales (8,9), changes due to rehabilitation interventions (10), and small fluctuations over time in several aspects of motor function (11,12), particularly gait and balance (7).

For example, indexes such as sway complexity and sway intensity can describe irregular and large trunk sway during static balance tests (13). Specifically, low sway complexity indicates increased sway smoothness and regularity and reflects the loss of complexity and adaptability of the balance control system due to the reduction and/or impairments of its structural components and their interaction (14). Besides, a larger sway intensity means an increased amplitude and velocity of trunk sway, indicating the difficulty for PwMS in maintaining a stable position and a center of mass far from the limits of the base of support (15). As for walking, a recently published framework identified a set of validated instrumental metrics relevant to describing the different domains of walking in MS, such as gait rhythm, stability, symmetry, and variability (16).

Current gaps and study rationale

To date, few longitudinal studies have independently examined the progression of cognitive decline, gait impairment, and balance deterioration over time (17-20). Galea et al. reported significant declines in gait and balance, even though PwMS did not experience clinical relapse over a 12-month period (20). Moreover, Damasceno et al. found that stable cognitive function over a two-year observation period was associated with better long-term outcomes (17).

However, no longitudinal cohort studies have been performed yet to assess both motor and cognitive functions using clinical and instrumented tools to detect changes over time. Given the importance of characterizing specific deficits, identifying subtle deteriorations caused by the progression of the disease, and optimizing treatment strategies, this study aimed at investigating short-term motor and cognitive trajectories in early diagnosed, non-disabled PwMS using a combination of clinical, subjective, and instrumented tools. We hypothesize that even in the early stages of MS, measurable functional deteriorations can be detected over time, which could help guide more personalized and effective treatment strategies.

Methods

Participants

We recruited a convenience consecutive sample of PwMS diagnosed following the McDonald criteria (21) from three Italian centers.

The inclusion criteria were: confirmed MS diagnosis, EDSS ≤2.5 (i.e., no locomotor disability), disease duration ≤5 years, stable disease course clinically defined as <0.5-point increase in the EDSS disability score over the last 3 months, age ≥18 years and ability to give written informed consent. We excluded participants with diagnoses of major depression, severe joint and/or bone disorders interfering with balance and gait (based on clinical records), and cardiovascular or other concomitant neurological diseases.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee. Each participant gave the informed consent to participate.

Procedures

Participants were examined at two time points, baseline and after 2 years. At each of the time points, participants underwent a neurological assessment for disability, performance tests, and patient-reported outcomes scales on different domains (i.e., endurance, walking, balance, upper limb, cognition). We used written and standardized instructions, and the same test order was used at both time points, asking

participants to complete all questionnaires before the clinical and instrumented assessments.

The whole assessment was performed in a single session, allowing PwMS to rest approximately 2-5 minutes after each mobility test based on PwMS' needs. When participants had an exacerbation on the day of the assessment, measurements were postponed until the exacerbation had subsided or complaints had stabilized.

Researchers with experience in MS administered the assessments and were trained in dedicated practice sessions to ensure standardization among centers.

Outcome Measures

Disability

Expanded Disability Status Scale (EDSS) that ranges from 0 (normal neurological signs) to 10 (death due to MS). In specific, when a subject is independent in walking, the score ranges between 0 and 4.5, depending on the distance walked, while a score from 5.0 to 9.5 describes an increased difficulty in walking (22).

Walking

The Six Minute Walking Test (6MWT) measures walking endurance. Participants were instructed to safely walk as fast as possible to cover a maximum distance in 6 minutes on a 30 m walkway with turns at both ends. We recorded the total distance covered during the 6MWT (23). Moreover, PwMS performed the 6MWT while wearing three wireless inertial sensors (MTw, XSens, NL) secured to the lower back, at L5 level, right and left shanks (see Angelini et al. for further details) (7). Each sensor consisted of a 3D accelerometer (±160 m/s 2 range), a 3D gyroscope (±1200 deg/s range), and a 3D magnetometer (±1.5 Gauss). Sensor signals were recorded at 75 Hz. We calculated: Stride regularity (increasing values from 0 to 1 indicate higher stride regularity); Gait instability (larger score means increased instability, as detailed in Caronni et al. (24); Gait symmetry (increasing values from 0 to 100% indicate more symmetrical gait); and Cadence (computed as 60/Tstride, where Tstride is the stride duration) (11).

Walking speed was measured with the Timed 25 Foot Walk (T25FW). Participants were asked to walk twice at a fast but safe walking speed, and the mean of the two trials was calculated. The Twelve-Multiple Sclerosis Walking Scale (MSWS-12) was administered to rate perceived walking ability. Each item was scored on a 1-5 scale; the higher the score, the higher the perceived walking difficulties (25).

Balance

The Fullerton Advanced Balance-Short version scale (FAB-S) is a 6-item balance scale with a 5-point ordinal scale (0-4) for each item. The maximum score on the scale is 24 points, with increasing scores meaning better balance performance. The FAB-S scale is suitable for comparing participants with high balance skills with other scales (26). The subjects executed the test wearing an inertial sensor (MTw, Xsens, NL) secured at the sternum level with an elastic band. Signals from the inertial sensor were acquired with a sampling frequency of 75 Hz. Sway Complexity and Sway Intensity metrics, defined by McCallum et al. (27) and detailed in Carpinella et al. (13), were calculated. Increasing values of Sway Complexity indicate higher adaptability and automaticity of the balance control system, while decreasing values of Sway Intensity represent smaller amplitude and velocity of trunk sway and, consequently, better standing balance.

Fatigue

The Fatigue Severity Scale (FSS) is a tool designed to assess the impact of fatigue on daily function. It consists of nine items related to fatigue. The maximum score is 7, which indicates a high level of fatigue (28).

Upper limb

To assess upper limb function, we used the Nine Hole Peg Test (NHPT) and Manual Ability Measure-36 (MAM-36). The NHPT measures manual dexterity, and the mean of two trials was considered (29). MAM-36 was used to rate perceived manual ability on a scale ranging from 0 (impossible to complete any activities) to 144 (every activity is accomplished without any difficulty) (30).

Cognition

To assess learning, memory, and processing speed in PwMS, we used the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). It is a cognitive battery composed of three tests: the Symbol Digit Modalities Test (SDMT) to assess information speed, the California Verbal Learning Test-II (CVLT) for verbal learning and memory, and the revised version of the Brief Visuospatial Memory Test (BVMT) for visuospatial memory (31).

Statistical analysis

Mean (SD) values or median (min-max) were used to describe the magnitude of functional disorders, and linear models were used to identify univariate and multivariate statistically significant differences between baseline and follow-up scores, taking into account confounders such as age, disease duration, education, and medication. We checked for residual distribution and the presence of influential points. In the case of non-normal distribution of residuals, we used robust linear models using MM methods. Moreover, percentages of abnormal scores according to normative values were used to report functional disorders at baseline and at 2-year follow-up. The McNemar test was computed to check the differences between these percentages. R v3.6.2 was used for data analyses. $p < 0.05$ was considered statistically significant.

Results

In this paper, we reported data on 63 out of 82 (3) participants who completed all the assessments within 2 years. Participants were mostly female (n = 37, 60%), and all had a relapsing-remitting MS phenotype. At baseline, 13% of PwMS were taking no MS- Disease Modifying Therapy

(DMT), 62% first line, and 25% second line. These percentages were slightly different after 2 years: 7% no MS-DMT, 50% first-line MS-DMT, and 43% second-line MS-DMT. In detail, 44 PwMS maintained the same medication at follow-up; 8 PwMS (taking no MS-DMT at baseline) were taking respectively first-line DMT (n = 3) and second-line DMT (n = 2). Moreover, 8 PwMS changed medication from first-line to second-line DMT, and one subject changed from first-line DMT to no MS-DMT. Clinical longitudinal data are detailed in Table 1.

TABLE 1 - Clinical longitudinal data at baseline and at follow-up after 2 years.

	Baseline (N = 63)	2-year Follow-up (N = 63)	Univariate Estimate (Basel vs FU); p-value; and 95% CI	Multivariate Estimate (Basel vs FU); p-value; and 95% CI
EDSS (points)*	2 (0-2.5)	1.5 (0-4.5)	0.07; 0.50; −0.15 0.30	−0.03; 0.18; −0.30 0.23
Age (years)	38.7 (10.7)	40.6 (10.8)	-	
Disease duration (years)	2.3 (1.8)	4.3 (1.9)	-	
Education (years)	14.8 (3.6)	14.8 (3.6)	-	
6MWT (m)	566.2 (80.4)	573.9 (94.7)	12.80; 0.06; −0.04 25.77	12.7; 0.51; −3.63 29.00
FAB_S (points)*	23 (14-24)	23.5 (13-24)	−0.29; 0.22; −0.77 0.18	−0.40; 0.98; −1.01 −0.21
FSS (points)*	2.89 (0.89-7)	2.67 (1-7)	−0.01; 0.89; −0.3 0.26	−0.04; 0.94; −0.38 0.29
T25FW (sec)	4.30 (0.82)	4.11 (1.16)	**−0.24;0.04; −0.47 -0.006**	−0.25; 0.9; −0.55 0.05
9HPT (sec)				
Dominant hand	20.3 (3.4)	19.0 (3.0)	−1.01; 0.001; −1.75 −0.41	-5.00; 0.04; -9.58 -0.21
Non-dominant hand	21.6 (4.5)	20.4 (3.6)	−1.0, 0.001; −1.66 −0.40	−1.10; 0.39; −6.32 2.53
MSWS-12 (points)*	25 (20-65)	25 (20-78.3)	−0.13; 0.88; −1.90 1.63	0.37; 0.17; −1.49 2.24
MAM-36 (points)*	144.0 (94-144)	138.48 (104-144)	−0.0001; 0.44; −0.0002 0.0001	−2.37; 0.37; −0.61 0.15
SDMT (points)	55.34 (14.7)	61.4 (15.5)	**6.11; <0.001; 3.61 8.61**	**6.6; 0.02; 3.53 9.67**
CVLT (points)	10.4 (3.6)	13.0 (3.5)	**2.65; <0.01; 1.95 3.36**	2.21; 0.41; 1.41 3.02
BWMT (points)	10.50 (3.53)	11.42 (3.21)	**2.62; 0.02; 0.12 2.15**	0.88; 0.55; −0.13 1.89

*Median (min-max); EDSS: Expanded Disability Status Scale; MS: Multiple Sclerosis; 6MWT: Six Minute Walk Test; FAB_S: Fullerton Advance Balance scale_Short; FSS: Fatigue Severity Scale; T25FW: Timed 25 Foot Walk Test; 9HPT: Nine Hole Peg Test; MSWS-12: Multiple Sclerosis Walking Scale Twelve; MAM-36: Manual Ability Measurement_36; SDMT: Symbol Digit Modalities Test; CVLT: California Verbal Learning Test; BWMT: Brief Visuo-spatial Memory Test; * using robust linear estimation methods

Clinical changes between baseline and follow-up

Median EDSS scores were reported in Table 1, showing no or mild improvements between baseline and 2-year follow-up. This was true also considering age, sex, education, and DMD_line as covariates that were statistically significantly ($p < 0.05$) associated with SDMT for Age: Beta = 0.04, P = 0.03, and Education: Beta = 0.23, P= 0.09.

However, we can observe a different EDSS distribution over the years (Fig. 1). To note, at baseline, all PwMS were lower than 2.5 EDSS points, while after 2-year 24% of them worsened on EDSS (EDSS change ≥ 0.5 points), 12% improved, and only 63% were stable. Considering a 1-point change in the EDSS, we observed 9 (14%) PwMS deteriorated and 7 (11%) PwMS improved.

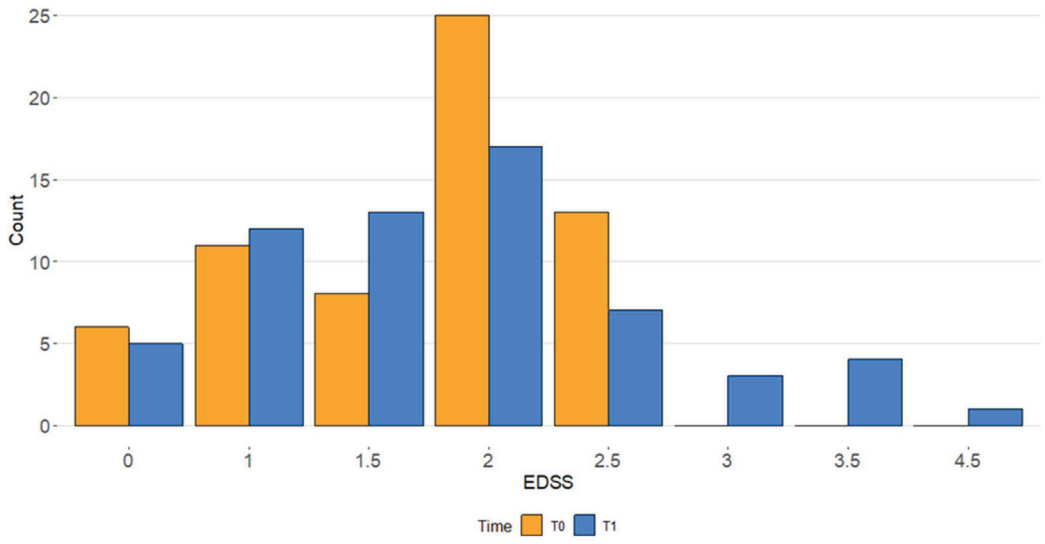

FIGURE 1 - Number of participants per different EDSS scores
EDSS: Expanded Disability Status Scale (EDSS); Count: number of PwMS; T0: Baseline; T1: Follow-up after 2 years

At baseline, MSWS-12 was the clinical measure showing the largest percentage of abnormal scores, with 60% of participants reporting perceived walking limitations (see also Supplementary Fig. 1). This percentage only slightly increased after 2 years (66%, p = 0.42).

When considering walking endurance, 27% of PwMS had an abnormal score in the 6MWT at baseline that significantly decreased after 2 years (13%, p = 0.03). Improvements were less evident for gait speed, with 18% of PwMS showing an abnormal score in the T25FWT at baseline and 14% at the 2-year follow-up (p = 0.68). This trend was reversed for balance with a percentage of abnormal score in the FAB_S of 46% at baseline and 49% after 2 years (p = 0.78, Fig. 2).

We did not observe changes in fatigue (FSS), with PwMS showing a percentage of 21% abnormal scores both at baseline and after 2 years (p = 0.99, Fig. 2).

One-third (33%) of PwMS showed abnormal NHPT scores at baseline that significantly decreased after 2 years (17%, p = 0.02). This reduced percentage of abnormal scores in manual dexterity was not accompanied by a higher percentage of abnormal scores in the perceived manual ability measured by the MAM-36 that significantly worsened from 35% at baseline to 48% at 2-year follow-up (p = 0.02, Fig. 2). In supplementary Figure 2. We also reported MAM-36 score at baseline and after 2 years, indicating worse performances on items more related to strength activities (ITEM 11: Wring a

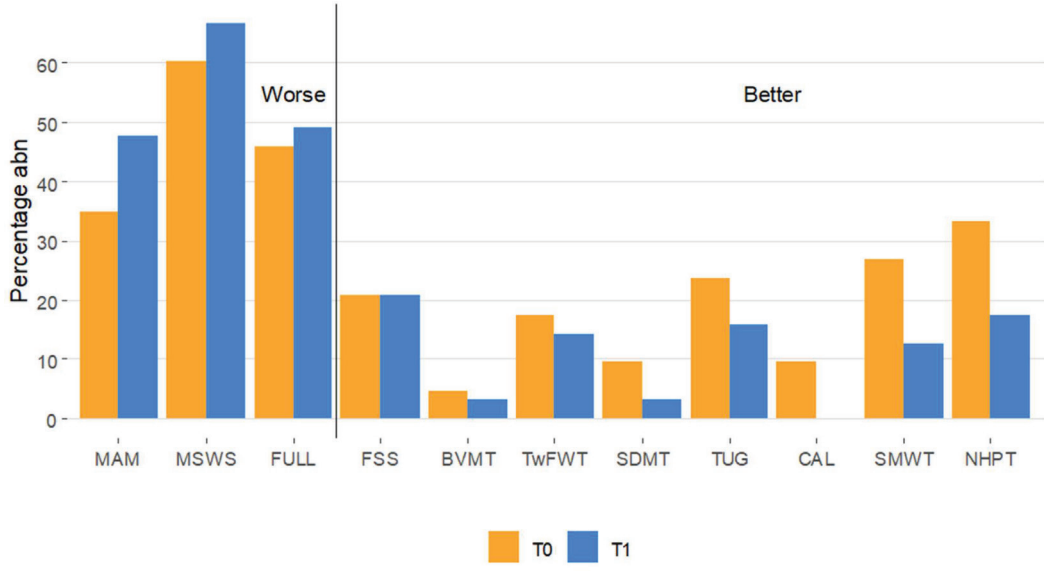

FIGURE 2 - Percentage of abnormal clinical scores at baseline and at follow-up
Percentage abn: Percentage abnormal scores; MAM: Manual Ability Measure-36; MSWS: Twelve-Multiple Sclerosis Walking Scale; FULL: Fullerton Advanced Balance_Short version scale; FSS: Fatigue Severity Scale; BVMT: Brief Visuospatial Memory Test TWFWT: Timed 25 Foot Walk; SMDT: Symbol Digit Modalities Test; TUG: Timed Up and GO; CAL: California Verbal Learning Test-II; SMWT: Six Minute Walking Test NHPT: Nine Hole Peg Test

towel; ITEM 16: Cut nails with a nail clipper; ITEM 26: Open a medication bottle with a child-proof top; ITEM 34: Use a hammer or screwdriver)

Unexpectedly, we did not find any relevant cognitive disorders at baseline. Indeed, they were the same or even better after 2 years: 10% had abnormal scores on the SDMT at baseline, 4% after 2-year (p = 0.22); 10% on the CVLT at baseline, 0% after 2-year (p = 0.13); and 5% on the BVMT at baseline, 3% after 2-year (p = 0.99, Fig. 2).

Instrumented changes between baseline and follow-up

As shown in Table 2, we observed statistically significant improvement in gait symmetry, stable results in cadence and gait regularity while stride length deteriorated when adjusting for covariates (Education: Beta = 0.01, P = 0.01)

Additionally, we obtained controversial results when considering static and dynamic balance indexes. Indeed, a statistically significant worsening of Sway Complexity during standing (i.e., reduced automaticity and adaptability of

TABLE 2 - Changes in instrumented balance and walking outcomes at baseline and 2-year follow-up

	Baseline	2-year Follow-up	Univariate Estimate (Basel vs FU); p-value; and 95% CI	Multivariate Estimate (Basel vs FU); p-value; and 95% CI
Static and dynamic Balance				
Complexity* (a.u.)	−0.15 ± 1.06	−0.38 ± 1.08	**−0.25, 0.001, −0.40 −0.10**	−0.22, 0.42, −0.41 −0.02
Intensity^ (a.u.)	0.00 ± 0.69	−0.17 ± 0.78	−0.22,0.06, −041 −0.02	**−0.10, 0.03, −0.25 0.06**
Gait Instability^ (a.u.)	0.67 ± 0.11	0.70 ± 0.13	**0.03, 0.04, 0.001 – 0.06**	0.05,0.34,0.021 0.09
Gait Quality				
Gait Symmetry* (a.u.)	80.24 ± 20.24	83.00 ± 8.85	**2.64, 0.001, 1.06 4.23**	2.58, 0.44, 0.40 4.76
Gait Regularity* (a.u.)	0.87 ± 0.07	0.88 ± 0.08	0.007, 0.28, -0.006 0.02	0.0002, 0.40, −0.018 0.018
General gait parameters				
Cadence* (stride/min)	63.79 ± 5.14	64.34 ± 5.77	0.56, 0.11, −0.14 1.27	0.25. 0.08, −0.65 1.15
Stride length* (m)	1.56 ± 0.19	1.54 ± 0.18	−0.02, 0.13, −0.05 0.006	**−0.02, 0.008 −0.06 0.01**

* Larger or ^ smaller values mean better performance

balance control) was accompanied by a statistically significant improvement in Sway Intensity (i.e., reduced amplitude and velocity of trunk sway). Regarding dynamic balance, Gait Instability showed a small worsening at a 2-year follow-up when adjusting for covariates (Disease duration: beta = 0.01, P = 0.04, Table 2). We found no statistically significant differences between baseline and 2-year follow-up in the percentage of PwMS showing abnormal values in static and dynamic balance: 27% had abnormal scores in sway complexity at baseline, 35% after 2-year (p = 0.18); 27% in sway intensity at baseline, 13% after 2-year (p = 0.06); and 51% on the gait instability at baseline, 57% after 2-year (p = 0.60, Fig. 3).

No differences were found in gait quality (Gait symmetry: 54% at baseline, 42% after 2-year; Gait regularity: 25% at baseline; 14% after 2-year, Fig. 3) and in general gait parameters (Cadence: 21% at baseline; 14% after 2-year; Stride length: 32% at baseline; 23% after 2-year, Fig. 3).

Discussion

In the present study, we evaluated functional changes over 2 years in a group of PwMS in the early phase of the disease, with no disability and fully able to walk. The first finding of this work highlights that the disability level remained stable in the majority of the sample over the years. Moreover, contrary to our initial hypothesis, also functional outcomes such as fatigue, upper limb, and cognition remained stable over the years. Finally, instrumented data showed mixed results, suggesting that it is still unclear whether instrumented variables could depict balance and gait changes in short-term follow-up.

One of the main results of the study is that the mean EDSS score remained stable over 2-years. Eighty-six percent of PwMS maintained a stable EDSS score, while 24% deteriorated, although they did not exceed the threshold for moderate disability, thus indicating a preserved walking ability. However, disability accrual observed in several subjects may indicate unfavorable disease progression, urging the development of predictive models to tailor interventions. Our data are in line with a previous study by Galea et al. that reported a worsening in 24% of subjects in a similar population of PwMS. (20) and other studies on DMT showed a stable course of the disease in most of the recruited participants in the years right after diagnosis (32). These results are corroborated by no changes in fatigue, upper limb function, and cognition at follow-up. This also holds for the percentage

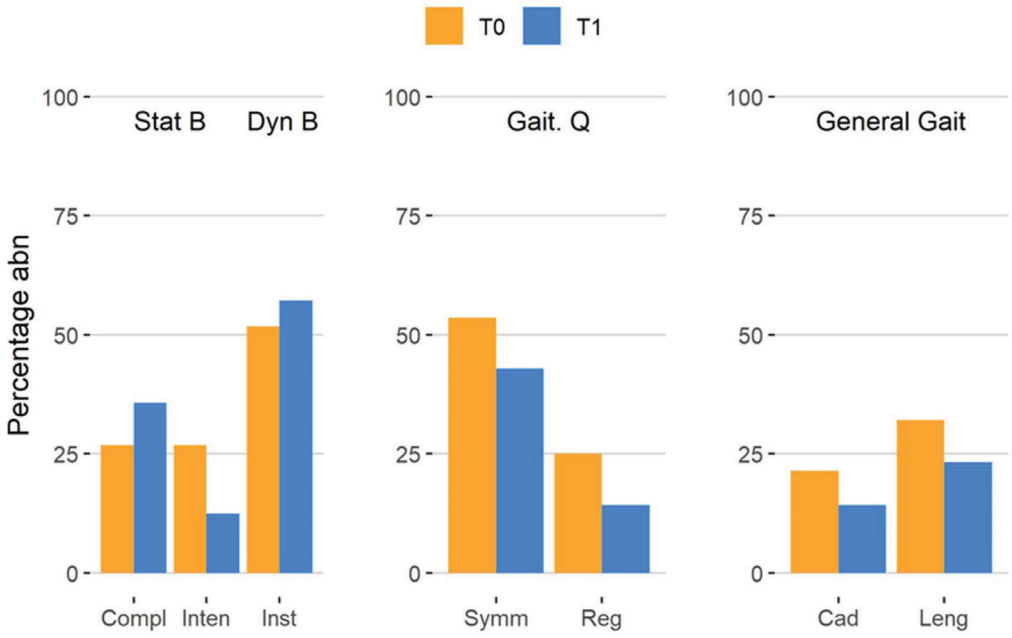

FIGURE 3 - Percentage of abnormal scores of instrumented variables at baseline and at follow-up
Stat B: Static Balance; Dyn B: Dynamic Balance; Compl: Complexity; Inten: Intensity; Inst: Instability; Gait Q: Gait Quality; Symm: Symmetry; Reg: Regularity; Cad: Cadence; Leng: Stride Length

of abnormal scores, which was unchanged across domains except for balance, perceived walking ability, and upper limb perception.

Our results obtained using a general measure of disability are parallel with changes we observed considering specific clinical scales. In our preceding cross-sectional study (3), we reported that fatigue was abnormal in 25% of PwMS; thus, we expected an increased percentage of PwMS affected by fatigue with a higher percentage of abnormal scores after two years. Surprisingly, fatigue remained stable in the majority of the sample, and only a few subjects worsened over the 2-year period, highlighting the stability of this symptom during this observational period. Our results are in agreement with other longitudinal studies. One by Damasceno et al. reported changes in fatigue over 2-year similar to our data (17). The other by Chang et al. that assessed 322 PwMS in the early phase reported no difference in fatigue after a short follow-up of 1-year. (33)

A lack of deterioration was also observed in the upper limb. Manual dexterity performances are similar between our sample and healthy subjects, indicating we assessed subjects that still did not show any upper limb dysfunction. Contrary to our expectation, we observed a statistically significant but no clinical improvement in hand performance at 2 years, possibly indicating that lack of manual dexterity impairments and test practice effects may have influenced our results on manual dexterity due to the repeated execution of the 9HPT. The lack of real clinical improvements in upper limb dexterity is confirmed by PRO data. Indeed, although we showed improvements in manual dexterity over the years, PwMS perception of the use of the upper limb during daily activity seemed to be unchanged. However, the relationship between perceived and objective deterioration should be considered in light of cross-sectional studies reporting there is a weak association between objective upper limb function and subjective perception in samples with an overall lower disability, while the association is strong when considering people with a higher level of disability (34). Interestingly, we observed that PwMS's perception was lower in activities more associated with strength (e.g., opening a bottle or wringing out a towel) than dexterity, indicating deficits more at the impairment level than functional level (see Supplementary Fig. 2).

Changes observed and perceived in motor function were accompanied by no sign of deterioration in cognition, especially in executive function, with a 6-point improvement over 2 years (35). Our results are in line with previous prospective studies reporting that (17,18,36) cognitive functions remained unchanged at short follow-ups, indicating that longer observations are crucial to understanding whether cognitive impairments are stable or are likely to progress.

Concerning mobility, around half of PwMS still had abnormal scores in balance tests that did not change compared to baseline assessment, confirming that balance disorder remains one of the most prevalent impairments in this population (3). Also, follow-up assessments still confirmed worse scores in tasks with body/head turns, highlighting the presence of somatosensory impairments (9). This is worth considering when planning rehabilitation interventions. In the specific gait, PwMS were faster (25FWT) at 2 years. However, this result was not confirmed by the endurance test, and subjective data showed a slightly higher percentage of abnormal scores on the perception of walking ability, indicating that the patient's perspective is different from the clinical tests in describing changes in gait.

Instrumented data on balance yielded controversial results since the worsening in Sway Complexity was

accompanied by an improvement in Sway Intensity during upright standing. We can speculate that worsening in sway complexity over the years indicates less automatic and more conscious postural control and the need for increased attentional investment to maintain balance (37). It could also be speculated that the lack of changes observed after 2 years is the result of compensatory mechanisms taking place to maintain balance at an optimal level. The assessment of cortical activity at the two time points may unveil these compensatory mechanisms.

Moreover, our longitudinal analysis of instrumented gait variables confirmed this trend of improvement in symmetry with a slight deterioration in stride length and gait instability. Our data are in line with a previous cross-sectional study by Kalron et al. (38) that observed no significant differences in gait variability in terms of step length, step time, step width, and single support in PwMS with low disability, while a statistically significant increase when PwMS reached higher level of disability. Similarly, our previous cross-sectional study on a subsample of the same population showed that PwMS who worsened in EDSS showed higher gait abnormalities (increased gait instability, decreased symmetry, and lower stride regularity) compared to stable PwMS confirming this association between high disability and gait abnormality (11). While our findings are consistent with these earlier studies, the longitudinal analysis of instrumented gait variables in this population represents a novelty, making direct comparisons with existing research challenging.

Taken together, the main point of this study is that a 2-year observation period is too short to reveal a deterioration of the disease at the functional level, suggesting that a longer timeframe and a deeper analysis at the impairment level should be considered to monitor MS functional deterioration and improvement. Moreover, It could also be speculated that the lack of changes observed after 2 years is the result of brain adaptation taking place to maintain functions at an optimal level. Specifically, we can postulate that the lack of changes at the behavioral level is due to compensatory brain mechanisms, which translate into bilateral recruitment or the involvement of areas not typically involved in motor control. The combined assessment of behavior and cortical activity at the two time points may unveil these compensatory mechanisms.

Strengths and limitations

The strength of this work is that we reported for the first time a comprehensive longitudinal picture of motor and cognitive disorders assessed both with clinical and instrumented tests in non-disabled PwMS. However, we should state some limitations. The first main limitation is that the follow-up period was too short to reveal deterioration in this population, although we did not address the potential for non-linear progression in early MS. Second, even if the follow-up was performed after 2 years, we tested cognition without providing different versions of the test. Third, we did not collect EDSS functional scores that could detail the impairment level of each subject. Fourth, our results are based on the analysis of a single cohort with a relatively small sample size that may limit the generalizability of findings and the precision of the estimations. Another limitation is the potential insufficient sensitivity of the tasks performed and the tools employed. More complex assessments, such as prolonged treadmill walking or the use of more advanced technologies (e.g., optoelectronic systems, electromyography, and force plates), could have enhanced the sensitivity of the evaluation. However, this would have compromised the ecological validity of the assessment, which was intentionally designed to closely approximate real-life conditions. Lastly, we did not specifically perform clinical scales aimed at assessing deficits at the impairment level.

Conclusion

Although our expectation was that PwMS performances would have worsened across domains after 2 years or, at least, we expected that the addition of instrumented assessment could depict subtle changes in balance and gait performances. However, our data showed functional stability of the disease after 2 years. To guide clinicians towards more personalized medicine, future research with larger cohorts, longer follow-ups, and biomarker assessments are needed. This will be crucial for the development of predictive models that can guide the selection of optimal interventions to mitigate the progression of the disease.

Disclosures

Conflict of interest: The authors declare that there is no conflict of interest.

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Ethical approval: The study was approved by the ethical committees of all three participating centers. Written informed consent was obtained from all participants. The project was conducted in accordance with the Declaration of Helsinki and with local ethical guidelines.

Author contributions: EG: conceptualization (lead); data curation (supporting); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (equal); project administration (lead); resources (lead); supervision (lead); writing review and editing (lead). CS: Conceptualization (equal); data curation (supporting); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (supporting); supervision (equal); writing review and editing (lead). DA: Data curation (equal); funding acquisition (supporting); investigation (supporting); methodology (supporting); supervision (supporting); writing review and editing (equal). RDG: Data curation (equal); investigation (supporting); writing review and editing (supporting). AT: Conceptualization (equal); data curation (supporting); funding acquisition (equal); investigation (equal); methodology (equal); project administration (supporting); resources (supporting); supervision (equal); writing review and editing (equal). GB: Conceptualization (equal); data curation (supporting); funding acquisition (equal); investigation (equal); methodology (equal); project administration (supporting); resources (supporting); supervision (equal); writing review and editing (equal). PC: Conceptualization (supporting); resources (equal); writing review and editing (equal). MR: Conceptualization (supporting); resources (equal); writing review and editing (equal). IC: conceptualization (lead); formal analysis (lead); investigation (equal); methodology (lead); software (lead); writing original draft (lead). DC:

conceptualization (lead); data curation (supporting); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (equal); project administration (lead); resources (lead); supervision (lead); writing review and editing (lead).

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