Detection of subtle gait disturbance and future fall risk in early multiple sclerosis

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Abstract

Objective

To test the hypothesis that higher-challenge gait and balance tasks are more sensitive than traditional metrics to subtle patient-reported gait dysfunction and future fall risk in early multiple sclerosis (MS).

Methods

Persons with early MS ($n = 185$; ≤ 5 years diagnosed) reported gait function (MS Walking Scale) and underwent traditional disability metrics (Expanded Disability Status Scale [EDSS], Timed 25 Foot Walk). Patients and healthy controls ($n = 50$) completed clinically feasible challenge tasks of gait endurance (2-Minute Walk Test), standing balance (NIH Toolbox), and dynamic balance (balance boards; tandem walk on 2 ten-foot boards of different widths, 4.5 and 1.5 in). MRI assessed global and regional brain volumes, total T2 lesion volume (T2LV), infratentorial T2LVs and counts, and cervical cord lesion counts. Falls, near falls, and fall-related injuries were assessed after 1 year. We examined links between all tasks and patient-reported gait, MRI markers, and fall data.

Results

Patients performed worse on higher challenge balance, but not gait, tasks compared with healthy controls. Worse patient-reported gait disturbance was associated with worse performance on all tasks, but only dynamic balance was sensitive to mild patient-reported gait difficulty. Balance tasks were more correlated with MRI metrics than were walking tasks or EDSS score. Thirty percent of patients reported either a fall or near fall after 1 year, with poor dynamic balance as the only task independently predicting falls.

Conclusions

Balance plays a leading role in gait dysfunction early in MS. Clinically feasible higher-challenge balance tasks were most sensitive to patient-reported gait, MRI disease markers, and risk of future falls, highlighting potential to advance functional outcomes in clinical practice and trials.

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Glossary

EDSS = Expanded Disability Status Scale; **FOV** = field of view; **IQR** = interquartile range; **MS** = multiple sclerosis; **MSFC** = MS Functional Composite; **MSIS-phys** = physical component of the MS Impact Scale; **MSWS** = MS Walking Scale; **RADIEMS** = Reserve Against Disability in Early MS; **TE** = echo time; **TR** = repetition time; **T2LV** = T2 lesion volume; **T25FW** = Timed 25 Foot Walk; **2MWT** = 2-Minute Walk Test.

Gait and balance disturbance are among the most frequent symptoms reported by persons with multiple sclerosis (MS) and are understandably of high concern to patients and clinicians alike.¹ Attempts to objectively measure gait in the physician's office and in the context of clinical trials have largely relied on the Expanded Disability Status Scale (EDSS) and the Timed 25 Foot Walk (T25FW).^{2–4} These metrics have widespread acceptance in the field, but they provide limited detection of more subtle gait dysfunction reported by patients, especially early in disease.^{5–9} Related to gait and balance, fall risk is a major health concern for persons with MS,^{10–17} but most research focuses on older, more disabled patients. A need exists for clinically feasible and reliable metrics sensitive to mild gait dysfunction and risk for future falls in patients with early MS.

Here, we investigated the sensitivity of traditional and clinically feasible higher-challenge tasks of gait and balance in a cohort of 185 patients with early relapsing remitting MS or clinically isolated syndrome. We assessed whether patient-reported gait changes and MRI metrics of disease burden were better detected by traditional examinations (e.g., EDSS, T25FW) or higher-challenge tasks. We tracked falls and fall-related injuries 1 year later to identify the best baseline predictors of future falls in this early MS cohort. This work seeks to identify performance metrics with improved sensitivity to subtle gait disturbance and fall risk and that correlate best with neuroimaging markers of MS disease. Results also more broadly advance our understanding of gait and balance disturbance in patients with early disease.

Methods

Participants

The Reserve Against Disability in Early MS (RADIEMS) cohort is a longitudinal study of risk and protective factors for disability in persons with early relapsing remitting MS or clinically isolated syndrome. Patients 20 to 50 years of age and diagnosed ≤ 5.0 years previously from 2 MS centers in New York City were enrolled between September 2016 and December 2017. Exclusions included pregnancy, clinical relapse within 6 weeks, nonproficiency in English, history of other neurologic condition, neurodevelopmental disorder, diagnosed learning disability (attention-deficit/hyperactivity disorder not excluded), schizophrenia, bipolar disorder, substance abuse disorder, or current major depressive disorder. Persons without major depressive disorder but with previous or current anxiety or depressive symptoms were included

because exclusion would reduce generalizability. Baseline data from this cohort and 50 healthy controls are presented here, as well as fall-related information reported by patients 1 year after baseline. Healthy controls were mostly friends and non-first-degree relatives of patients to maximize demographic similarities. There were no differences between patients and healthy controls in demographic characteristics (table 1). As outlined in the Statistical Analysis section, the sole purpose of the healthy control group in this investigation was to assess differences between patients and healthy controls in 3 higher-challenge performance metrics of gait and balance. All other analyses were conducted in patients alone (e.g., links between performance and MRI metrics and falls).

Standard protocol approvals, registrations, and patient consents

The study was approved by local Institutional Review boards, and written informed consent was obtained from all participants.

Traditional measures of MS disability

Traditional measures of overall MS neurologic disability (EDSS) and gait speed (T25FW) were administered to patients with MS (not healthy controls). The EDSS and the T25FW are the gold standard measures of physical disability and gait in MS clinical trials. The T25FW is the gait component of the MS Functional Composite (MSFC),^{4,18,19} which is often the secondary disability outcome in MS clinical trials. The MSFC also assesses cognition (Symbol Digit Modalities Test) and upper extremity function (9-Hole Peg Test), which were included herein for completeness. T25FW and 9-Hole Peg Test were adjusted for age, sex, height, and weight. The Symbol Digit Modalities Test was adjusted for age, sex, and education.

Challenge tests of gait and balance

The following 3 higher-challenge tasks of gait and balance were completed by patients and healthy controls. Performance on all tasks was adjusted for age, sex, height, and weight.

NIH Toolbox 2-Minute Walk Test (2MWT)²⁰ assesses the maximal distance a person can walk within a 2-minute time limit. A 50-ft flat course was used, with orange cones placed at each end. Participants wore comfortable shoes and were asked to walk as quickly as possible back and forth between these cones. The total distance walked was measured in feet. Data for the 2MWT were missing for 2 healthy controls due to time constraints. Scores for these 2 participants were imputed on the basis of the mean distance for the healthy group. The 2MWT was not attempted by 2 patients with MS who

Table 1 Sample characteristics

	Persons with MS	Healthy controls	Statistic, <i>p</i> value
Sample size, <i>n</i> ^a	184	50	
Age (mean ± SD), <i>y</i>	34.3 ± 7.5	32.9 ± 7.5	<i>t</i> = 1.19, <i>p</i> = 0.234
Sex, M/F, <i>n</i>	61/123	18/32	χ^2 = 0.14, <i>p</i> = 0.706
Body mass index, %			χ^2 = 3.81, <i>p</i> = 0.283
<18.5 kg/m ² : underweight	2.7	4.0	
18.5–24.9 kg/m ² : normal weight	45.1	48.0	
25.0–29.9 kg/m ² : overweight	30.4	38.0	
>30.0 kg/m ² : obese	21.7	10.0	
Disease course (RRMS/CIS), <i>n</i>	164/20		
Years since diagnosis, median (IQR)	2.0 (0.9–3.3)		
Years since first symptom, median (IQR)	2.8 (1.4–4.6)		
EDSS score, ^b median (IQR)	1.0 (0.0–1.5)		
EDSS score, <i>n</i>			
0.0	63		
1.0	52		
1.5	34		
2.0	21		
≥2.5	15		
FSS	0	1	≥2
Visual FSS, <i>n</i>	150	23	11
Brainstem FSS, <i>n</i>	173	8	3
Pyramidal FSS, <i>n</i>	121	55	8
Cerebellar FSS, <i>n</i>	163	19	2
Sensory FSS, <i>n</i>	147	23	14
Bowel and bladder, <i>n</i>	137	40	7
Ambulation, <i>n</i>	180	2	2
MSWS categories, <i>n</i> (%)			
Minimal (0–25)		126 (68.5)	
Mild (26–49)		39 (21.2)	
Moderate-severe (50–100)		19 (10.3)	
Falls: month 12 after baseline, <i>n</i> (%)			
None		153 (83.2)	
1 Fall		21 (11.4)	

Table 1 Sample characteristics (*continued*)

≥2 Falls	10 (5.4)
Near falls: month 12 after baseline, <i>n</i> (%)	
None	143 (77.7)
1–3	29 (15.8)
≥4	12 (6.5)
Fall-related injuries: baseline to 1 <i>y</i> , <i>n</i> (%)	
None	134 (72.8)
≥1	50 (27.2)
T2 lesion outcomes, median (IQR)	
Total T2LV, mL	1.5 (0.6–4.4)
Infratentorial T2LV, mL	0.4 (0.0–0.2)
Infratentorial T2 lesion count	1.0 (0.0–4.0)
Cervical spine T2 lesion count	1.0 (0.0–3.0)
Normalized MRI volumes, mean ± SD, mL	
Total brain	1,553.6 ± 71.5
Total gray	804.7 ± 47.5
Thalamus	21.2 ± 1.7
Basal ganglia	27.2 ± 2.5
Cerebellar gray	102.5 ± 13.4

Abbreviations: CIS = clinically isolated syndrome; FSS = Functional System Score; IQR = interquartile range; MS = multiple sclerosis; RRMS = relapsing remitting MS; T2LV = T2 lesion volume.

^a One of the 185 patients was excluded from analyses due to body mass index >60 kg/m², which represented a notable confound in the interpretation of balance and gait function. Two patients were not permitted to undergo research MRIs due to metal in their bodies; therefore, they were excluded from neuroimaging analyses.

^b EDSS scores did not include the cerebral FSS (fatigue, mood, cognition) in an attempt to capture a pure physical metric of MS disability. Fatigue, mood, and cognition are captured independently by the FSS, Mental Health Inventory, Beck Depression Inventory–Fast Screen, and Symbol Digit Modalities Test.

reported inability to perform the task due to fatigue. These 2 patients were assigned the same distance as the lowest performer within the MS group.

NIH Toolbox Standing Balance Test²⁰ assesses postural sway with an iPod accelerometer during each of five 50-second stances. In the first 4 stances, participants remained as still as possible with feet together and arms crossed while standing (1) on the floor with eyes open, (2) on the floor with eyes closed, (3) on a foam pad with eyes open, and (4) on a foam pad with eyes closed. In the fifth stance participants stood (5) in tandem stance on floor with arms crossed and eyes open. If a participant was unable to hold the stance (i.e., stepped off), they were given a second attempt. Performance was quantified as a theta score representing stability across the 5 stances (higher is better). Due to technical difficulty, theta scores were missing for 1 patient and 2 healthy controls. These participants were assigned the mean theta score for their group.

Balance boards

On the basis of prior work in persons with orthopedic injuries,²¹ participants were asked to perform tandem walks on narrow boards with arms crossed on the chest. The lower-challenge board was 4.5 in wide and 0.75 in high; the higher-challenge board was 1.5 in wide and 1.5 in high. Each board was 10 ft long and marked into four 2.5-ft quarters. All participants wore standard flat-soled Keds-style sneakers. Participants performed 1 practice trial and 3 test trials on the lower-challenge board. Scores were recorded as the number of quarters completed before stepping off the board or removing arms from the chest. If a participant completed at least one-quarter on the lower-challenge board, she/he advanced to the higher-challenge board, and the same procedures were repeated. The score was calculated as percent of completed quarters across 3 test trials of each board (total quarters/24). Scores were adjusted for age, sex, height, and weight. The internal consistency (reliability) of balance board performance across trials was good (Cronbach $\alpha = 0.794$). A very high-challenge 0.75-in-wide board was also attempted, but this was excluded from analyses due to a floor effect, as indicated by medians of 0 (interquartile range [IQR] 0–1) for patients and 1 (IQR 0–2) for healthy controls.

Patient-reported gait disturbance

Patients reported gait disturbance on the MS Walking Scale (MSWS-12)⁵ at baseline. Patients were divided into minimal, mild, and moderate to severe gait difficulty according to published guidelines.²² To reduce potential confusion associated with these similar-sounding terms, we have renamed these gait disturbance classifications as none, mild, and high. The MSWS-12 was not completed by healthy controls.

MRI markers of disease burden

MRI sequences

Patients underwent the following 3D 3.0T MRIs (Siemens Skyra, Erlangen, Germany) of the brain: T1-weighted (repetition time [TR] 2,400 milliseconds, echo time [TE] 2.0 milliseconds, flip angle 8°, field of view [FOV] 256 mm, 176 contiguous slices, voxel size 1.0 mm³), T2-weighted (TR 3,200 milliseconds, TE 566.0 milliseconds, FOV 230 mm, 224 slices with 0.9-mm thickness, voxel size 0.9 mm³), and fluid-attenuated inversion recovery (TR 5,000 milliseconds, TE 387.0 milliseconds, FOV 230 mm, voxel size 0.4 × 0.4 × 0.9 mm) imaging. Patients also underwent the following images of the cervical spine in the same scanner: short TI inversion recovery (TR 3,116 milliseconds, TE 44.0 milliseconds, fifteen 3.0-mm sagittal slices) and T2-weighted (TR 2,800 milliseconds, TE 84.0 milliseconds, thirty 1.5-mm sagittal slices) imaging. Patients received all MRIs on entry into the study. MRI data from healthy controls were not used in the current investigation.

MRI outcomes

T2 lesion volumes (T2LVs) were derived from T2-weighted images using a local thresholding segmentation technique (Jim 6.0, Xinapse System, West Bergholt, Essex, UK) by

trained neuroimaging fellows, with adjudication by a neurologist. Total T2LV was recorded, as well as separate volumes for infratentorial T2LV consisting of lesion volumes within the cerebellum and brainstem. T2 lesion counts were quantified separately for the brainstem and cerebellum, which were added to derive a total infratentorial T2 lesion count, by a board-certified neurologist/MS fellow (O.A.) using fluid-attenuated inversion recovery and T2-weighted images. The same rater quantified T2 lesion counts within the cervical spinal cord from short TI inversion recovery and T2-weighted images of the cervical spine. Lesion counts were confirmed by a second rater (board-certified MS neurologist, S.C.K.), and any differences were resolved by consensus. Both raters were blinded to patient performance. Normalized volumes of total brain, total gray matter, thalamus, and basal ganglia (sum of caudate, putamen, pallidum) were measured with SIENAX²³ and FIRST²⁴ (parts of FSL²⁵) using lesion-filled T1-weighted images and applying the volume-scaling factor to adjust for intracranial volume. Normalized cerebellar gray matter was derived from FreeSurfer 5.0 using the same T1-weighted images, with adjustment for intracranial volume. MRI outcomes chosen for this investigation consisted of well-established estimates of global disease-related changes (e.g., total brain volume, total T2LV) and measures expected conceptually to relate to gait and balance deficits (e.g., infratentorial lesions, cerebellar volume).

Fall risk 1 year later

One year after baseline, all patients completed an electronic survey (via REDCap) assessing falls, near falls, and fall-related injuries. The question on falls read, “A FALL is when you end up ON THE FLOOR or GROUND because you lost your balance, you tripped, or your legs fell out from under you. You may or may not have been hurt. How often during the PAST MONTH have you had a FALL?” Responses were 0, 1, 2, 3, 4, and ≥ 5 . The question on near falls read, “A NEAR-FALL is when you lose your balance or stumble and almost fall, but you stop yourself from having a FALL. For instance, you grab onto someone for support or steady yourself against a wall. If you did not catch yourself, you would have fallen. How often during the PAST MONTH did you have a NEAR-FALL?” Responses were none, 1 to 3 times per month, 1 to 2 times per week, 3 to 6 times per week, 1 to 2 times per day, and ≥ 3 per day. We surveyed falls and near falls during the prior month (rather than year) to reduce recall bias. Lastly, we asked about fall-related injuries during the last year. We used the time frame of 1 year (rather than 1 month) because we expected fall-related injuries to be more memorable. Separate questions were asked about serious injuries (e.g., bone fractures, torn ligaments), moderate injuries (e.g., sprained ankle, gash requiring stitches), and minor injuries (e.g., bruises, cuts, pain lasting >24 hours). This assessment of patient-reported falls and injuries was not completed by the 50 healthy controls.

Other relevant patient reports

We assessed other patient-reported symptoms at baseline that may have predicted future fall risk, including fatigue assessed

with the Fatigue Severity Scale, mood assessed with the Mental Health Inventory and Beck Depression Inventory–Fast Screen, and physical disability assessed with the physical component of the MS Impact Scale (MSIS-phys). The MSWS-12 and MSIS-phys were log-transformed as appropriate due to notable skewedness.

Statistical analysis

Disability on traditional metrics (EDSS, T25FW) is reported. Normality of performance metrics was assessed with Kolmogorov-Smirnov and Shapiro-Wilks tests, which determined subsequent use of parametric or nonparametric analyses. We used *t* tests or Mann-Whitney *U* tests to assess differences between patients and healthy controls on higher-challenge tasks (2MWT, NIH Balance, balance boards; adjusted for age, sex, height, weight). Adjustment of performance for age, sex, height, and weight was accomplished by saving unstandardized residuals for each participant from general linear models run with the performance metric as the dependent variable and covariates entered. Residuals were added to the mean raw performance of the sample. This was performed separately for each performance metric. For patient-reported gait and performance metrics, we used analyses of variance or Kruskal-Wallis tests with follow-up Mann-Whitney *U* tests to investigate performance differences on quantitative gait and balance tasks (T25FW, 2MWT, NIH Balance, balance boards) across levels of patient-reported gait disturbance (MSWS-12: none, mild, high). Healthy controls were then added as an additional comparison for all tasks except T25FW. Corrections were made for multiple comparisons (21 pairwise comparisons, Bonferroni $p = 0.0024$). For MS disease burden and performance metrics, we used 2-tailed Spearman correlations to assess relationships between performance metrics and MRI markers. Corrections were made for multiple comparisons (78 pairwise comparisons, Bonferroni $p = 0.00064$). For falls, data on falls, near falls, and injuries are reported. Differences in performance metrics between patients who did and those who did not report falls or falls/near falls were assessed. In a series of 3 stepwise logistic regressions (entry $p = 0.05$, removal $p = 0.10$), we predicted future fall occurrence with baseline (1) performance metrics, (2) performance metrics and patient-reported function, and (3) performance metrics, patient-reported function, and MRI markers. This strategy sought to identify the most sensitive performance metrics but also to investigate whether performance metrics contribute to falls independently of patient report and neuroimaging. The same procedures were used to assess differences between patients who did and those who did not report falls or near falls. Statistical analyses were performed with SPSS version 24 (SPSS Inc, Chicago, IL).

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Traditional measures of disability in patients with MS

This early MS cohort had low disability as assessed by the EDSS (median 1.0, IQR 0.0–1.5, table 1), and gait speed on the T25FW was normal (median 4.05 seconds, IQR 3.70–4.44 seconds) relative to published healthy data (4.3–4.4 seconds).¹⁹ Only 10 patients had T25FW scores ≥ 5.0 seconds, with only 2 patients ≥ 6.0 seconds and no patients ≥ 7.0 seconds. Despite low disability and normal gait speed, 31.5% of patients reported at least mild gait disturbance: 68.5% none, 21.2% mild, and 10.3% high. Moreover, 24.2% of patients with EDSS scores ≤ 1.5 endorsed at least mild gait disturbance (36 of 149).

Higher-challenge performance metrics: patients with MS vs healthy controls

Performance metrics were not normally distributed (Kolmogorov-Smirnov and Shapiro-Wilks $p < 0.05$), so non-parametric statistics were used. Medians and IQRs are reported. There was no difference in distance (feet) walked between patients (664.15 ft; 612.43–707.62 ft) and healthy controls (668.12 ft; 616.93–710.22 ft) on the 2MWT ($U = 4,382.0$, $p = 0.608$, $d = 0.07$). In contrast, postural sway (theta) during the NIH Standing Balance Test was worse among patients (0.677; 0.327–0.981) than controls (0.939; 0.642–1.148; $U = 3,281.0$, $p = 0.002$, $d = 0.42$), and dynamic balance (percent completed) during tandem walking on the balance boards was much worse among patients (0.586; 0.478–0.692) than controls (0.713; 0.578–0.817; $U = 2,889.0$, $p < 0.0001$, $d = 0.55$).

Patient-reported gait disturbance and performance outcomes

Worse patient-reported gait disturbance was associated with worse performance on all tasks ($p < 0.001$), although the relationship with T25FW was weakest (table 2). Pairwise comparisons with Mann-Whitney *U* tests revealed that all tasks discriminated between patients reporting high vs no and high vs mild gait disturbance (figure). All comparisons withstood corrections for multiple comparisons (Bonferroni $p = 0.0024$) except for T25FW between mild vs high gait disturbance. Only balance board walking ($p = 0.010$) and 2MWT ($p = 0.037$) discriminated between patients reporting no and those reporting mild gait difficulty, although neither withstood correction for multiple comparisons. When healthy controls were added as an additional comparison group, performance on balance boards ($p < 0.001$) and NIH Standing Balance assessment ($p = 0.004$) were the only metrics that discriminated between healthy controls and patients reporting mild gait disturbance, and only balance board performance withstood correction for multiple comparisons.

Relationships with MRI markers of MS disease burden

MRI markers of MS disease burden were much more strongly correlated with performance on balance tasks than walking

Table 2 Performance differences across levels of patient-reported gait

Performance metric Kruskal-Wallis tests	Gait disturbance (MSWS-12)	Median	IQR
T25FW, s; $\chi^2[2] = 14.07, p < 0.001, d = 0.58$	None	4.00	3.71 to 4.28
	Mild	4.16	3.71 to 4.53
	High	4.46	4.16 to 5.07
2MWT, ft; $\chi^2[2] = 23.92, p < 0.001, d = 0.77$	None	673.25	638.59 to 721.01
	Mild	650.26	618.82 to 698.75
	High	575.97	550.81 to 625.40
Healthy control comparison		668.12	616.93 to 710.22
NIH BALANCE (theta); $\chi^2[2] = 25.30, p < 0.001, d = 0.80$	None	0.872	0.509 to 1.006
	Mild	0.646	0.392 to 0.950
	High	-0.123	-0.735 to 0.387
Healthy control comparison		0.939	0.642 to 1.148
Balance boards, %; $\chi^2[2] = 21.65, p < 0.001, d = 0.73$	None	0.620	0.510 to 0.728
	Mild	0.545	0.422 to 0.655
	High	0.463	0.147 to 0.463
Healthy control comparison		0.713	0.578 to 0.817

Abbreviations: IQR = interquartile range; MSWS-12= Multiple Sclerosis Walking Scale; T25FW = Timed 25 Foot Walk; 2MWT = 2-Minute Walk Test.

tasks and the EDSS (table 3). In fact, balance board performance was related to nearly every MRI metric, and almost all links withstood correlations for multiple comparisons. There were no correlations of $p \leq 0.01$ between T25FW and any MRI metric, and no links withstood multiple-comparisons corrections. Note that patient-reported gait disturbance was more related to MS disease than was T25FW performance.

Predictors of future falls

Falls

About 1 in 6 patients (16.8%) reported a fall in the month before the 1-year follow-up survey. All baseline performance metrics were worse among patients subsequently reporting falls, with the largest difference for the balance boards (table 4). All metrics except EDSS withstood corrections for multiple comparisons ($p < 0.01$). Logistic regressions identified poor balance board performance as the best performance metric predicting falls (table 5). To add context to balance board findings, 51.6% of patients reporting falls (16 of 31) were unable to complete the wide board perfectly on all trials (vs 21.6% [33 of 153] in patients without falls), and 41.9% (13 of 31) were unable to walk the wide beam perfectly at least once (vs 2.6% [4 of 153] in patients without falls). The full model considering all predictors (performance, patient report, MRI) identified poorer balance board performance, worse patient-reported physical function (MSIS-phys), and lower thalamic volume as independent predictors of falls (table 5).

Falls or near falls

Thirty percent of patients (55 of 184) reported either a fall or a near fall at 12 months after baseline. All baseline performance metrics were worse among patients subsequently reporting falls or near falls ($p < 0.01$, except T25FW $p = 0.016$), with the largest difference for the balance boards (table 4). All metrics except T25FW withstood corrections for multiple comparisons ($p < 0.01$). Logistic regressions identified poor balance board

performance as the best performance metric predicting falls and near falls (table 5). Again putting findings in context, 43.6% (24 of 55) of patients with a fall or near fall were unable to complete the wide board perfectly on all trials (vs 19.4% [25 of 129] in patients without falls or near falls), and 27.3% (15 of 55) were unable to walk the wide beam perfectly at least once (vs. 1.6% [2 of 129] in patients without falls or near falls). The full model considering all predictors (performance, patient report, MRI) identified poorer balance board performance, worse patient-reported physical function (MSIS-phys), and lower thalamic volume as independent predictors of falls and near falls.

Injuries

We assessed injuries to characterize the deleterious consequences of falls. One-quarter of patients (25.0%, 46 of 184) reported at least 1 minor fall-related injury within the year after baseline, with 8.2% (15 of 184) reporting ≥ 3 minor fall-related injuries (table 1). Notably, 8 patients (4.3%) within this early disease cohort reported a serious or moderate injury in the past year, including fractured tibia and fibula ($n = 1$), fractured tibia ($n = 1$), fractured finger ($n = 1$), sprained wrist ($n = 2$), sprained ankle ($n = 2$), and torn rotator cuff ($n = 1$).

Supplemental analysis

Performance on the balance boards was presented as the percent of successfully completed quarters because measurement of larger units (2.5-ft quarters) was considered more clinically feasible than more precise measurement of smaller units (i.e., inches). We did, however, record the number of inches completed, which was almost perfectly correlated with quarters ($r = 0.990, \rho = 0.990$). To be thorough, we reran all analyses substituting percent of inches completed for percent of quarters. There were no meaningful changes in any results (consistent with the near-perfect correlation between measurements).

Figure Patient-reported gait and performance metrics

Performance for each task is compared across level of patient-reported gait dysfunction (none, mild, high). Significant differences between levels is displayed as red ($p \leq 0.001$), blue ($p \leq 0.01$), or green ($p \leq 0.05$). Data from healthy controls were added as a reference for each task except Timed 25 Foot Walk (T25FW), which was not completed in controls. The balance board task was the only metric that discriminated among every possible pairwise comparison and patients with mild gait disturbance from both healthy controls and patients with no gait disturbance. For 2-Minute Walk Test (2MWT) and NIH Balance, numbers beside 2 data points indicate frequency of patients with the same value. MS = multiple sclerosis.

We did not assess falls in our aforementioned healthy control group, but to provide context for patient fall results, we conducted an anonymous Institutional Review Board-exempt REDCap survey assessing falls and near falls in 100 healthy persons (same survey in Methods). We used data from the first 33 men and 67 women reporting no history of neurologic disease, no first-degree relative with MS, and no current pregnancy. Age (32.8 ± 7.7 years) and body mass index (25.2 ± 5.7 kg/m², based on reported height and weight) were similar to those in our MS cohort. Five healthy persons reported falls (5%), which was fewer than the 16.8% of patients reporting falls (Fisher exact $p = 0.0045$). Fewer healthy controls reported any falls or near falls (17%) compared with patients (29.9%; Fisher exact $p = 0.0219$).

We noted above that 4 values for 2MWT and 3 values for NIH Balance were missing and imputed across the patient and healthy control groups. All aforementioned results remained when these

participants were excluded from analyses. We assessed for collinearity among variables in the logistic regressions predicting falls and falls/near falls. There was no concern that collinearity affected results with 1 minor exception: MSIS-phys and MSWS-12 were collinear and about equally correlated with falls and falls/near falls. Results are therefore best interpreted as showing that baseline patient-reported physical function independently predicts fall risk, but we cannot interpret the relative importance of the general MSIS-phys over the more gait-specific MSWS-12.

Discussion

Persons with early MS frequently report subtle gait and balance decline, which clinicians often do not detect in the office by use of traditional examinations such as the EDSS and T25FW. Our results show that the addition of distance gait and especially higher-challenge balance tasks better capture these subjective

Table 3 Correlations between performance metrics and MRI markers of MS disease

	EDSS	T25FW	2MWT	NIH Balance	Balance boards	MSWS-12
T2LV total	0.097	0.165 ^d	−0.337 ^a	−0.275 ^a	−0.347 ^a	0.252 ^a
T2LV infratentorial	0.134	−0.015	−0.148 ^d	−0.197 ^c	−0.245 ^b	0.097
T2LV cerebellum	0.129	0.004	−0.098	−0.246 ^b	−0.295 ^a	0.181 ^c
T2LV brainstem	0.154 ^d	0.046	−0.180 ^d	−0.102	−0.185 ^d	0.061
Infratentorial T2 lesion count	0.234 ^b	0.132	−0.197 ^c	−0.251 ^a	−0.354 ^a	0.162 ^d
Cerebellar T2 lesion count	0.233 ^c	0.156 ^d	−0.239 ^b	−0.285 ^a	−0.359 ^a	0.185 ^d
Brainstem T2 lesion count	0.209 ^c	0.096	−0.187 ^d	−0.183 ^d	−0.309 ^a	0.145
Cervical spine lesion count	0.254 ^a	−0.051	−0.003	−0.128	−0.265 ^a	0.123
Brain volume	−0.028	−0.159 ^d	0.242 ^b	0.237 ^b	0.308 ^a	−0.270 ^a
Gray volume	−0.090	−0.188 ^d	0.252 ^a	0.263 ^a	0.341 ^a	−0.231 ^c
Thalamus volume	−0.130	−0.118	0.237	0.232 ^c	0.309 ^a	−0.210 ^c
Basal ganglia volume	−0.085	−0.098	0.289 ^a	0.395 ^a	0.333 ^a	−0.177 ^d
Cerebellar gray volume	0.028	−0.094	0.120	0.080	0.039	−0.052

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; MSWS-12 = MS Walking Scale; T2LV = T2 lesion volume; T25FW = Timed 25 Foot Walk; 2MWT = 2 Minute Walk Test.

^a $p < 0.00064$. Values withstood corrections for multiple comparisons (Bonferroni $p < 0.00064$).

^b $p \leq 0.001$

^c $p \leq 0.01$.

^d $p < 0.05$.

deficits. Specifically, measurement of dynamic balance with the balance board task best discriminated between patients and healthy controls and was the only performance metric sensitive to mild patient-reported gait changes. It was also most sensitive to risk for future falls and falls/near falls after 1 year. Balance tasks correlated with MS disease burden (e.g., infratentorial lesions) much more than the EDSS or T25FW, highlighting balance dysfunction as an early disease-related deficit and a major contributor to gait difficulties in early MS.

Persons with MS may exhibit a wide array of gait abnormalities (e.g., decreased step length^{26,27} and cadence^{27,28}), which can include reduced speed,²⁷ poor endurance,²⁹ and overall poorer mobility.³⁰ Proposed mechanisms for such gait dysfunction include sensorimotor impairment with resultant proprioceptive deficits and imbalance, lower extremity weakness and spasticity, or even frank cerebellar ataxia.³¹ Standardized clinical metrics have been used to quantify such impairment with varying degrees of success. Ample previous work has demonstrated the failure of EDSS alone to capture subtle dysfunction; incipient gait impairment has been identified in patients without measured EDSS pyramidal dysfunction.²⁶ In addition, the T25FW is less likely to identify disability or to detect ambulatory changes in patients with MS with overall minimal disability.^{8,9} In our patients with early MS, subjective report of gait disturbance (MSWS) was much more related to radiographic MS disease burden and balance task performance than was the T25FW. This again indicates that the T25FW is not sensitive to disease-related

changes in gait experienced by patients with early MS. Various clinical balance and ataxia scales have been tested in MS cohorts and measured for potential correlation with EDSS or ability to predict falls, but results have been inconsistent and have not been applied to early MS cohorts with low overall disability.^{32,33}

As noted, our data demonstrate that balance impairment notably contributes to ambulatory dysfunction early in MS. These results align with previous work demonstrating that persons with MS exhibit several abnormalities of balance control (e.g., decreased ability to maintain position, slow movement toward limits of stability, and delayed responses to postural displacements), which all contribute to gait dysfunction and increased fall risk.³⁴ The underlying mechanisms contributing to imbalance (and resultant gait dysfunction) may vary by individual, but we found that infratentorial lesions best predict balance. The influences of each system (e.g., sensorimotor, cerebellar) may also change over time as disease progresses. For instance, pyramidal dysfunction may begin to predominate later in disease course, as exhibited by improved sensitivity of the speeded walk tests in these populations to discriminate between varying levels of disability.⁹

Current understanding of fall prevalence in MS originates largely from studies of older and more disabled patients showing that >50% of persons with MS report falls in a 6-month period with high rates of fall-related injury.^{10–15} Our data highlight that falls are a significant concern even in early

Table 4 Differences in baseline performance metrics by future fall risk

Performance metric	Fall	Median	IQR
EDSS score $U = 1747, p = 0.017, d = 0.346$	No Yes	1.0 1.5	0.0 to 1.5 0.0 to 2.0
T25FW, s $U = 1,588, p = 0.004, d = 0.437$	No Yes	4.03 4.23	3.70 to 4.35 3.96 to 4.76
2MWT, ft $U = 1,344, p < 0.001, d = 0.584$	No Yes	668.2 619.8	630.4 to 713.0 574.1 to 660.2
NIH Balance, theta $U = 1,427, p < 0.001, d = 0.533$	No Yes	0.844 0.384	0.494 to 1.002 -0.123 to 0.904
Balance boards, % $U = 1,312, p < 0.001, d = 0.603$	No Yes	0.605 0.433	0.505 to 0.706 0.147 to 0.600

Performance metric	Fall or near fall	Median	IQR
EDSS score $U = 2,499, p = 0.001, d = 0.481$	No Yes	1.0 1.5	0.0 to 1.5 0.0 to 2.0
T25FW, s $U = 2,749, p = 0.016, d = 0.362$	No Yes	4.03 4.15	3.70 to 4.33 3.95 to 4.56
2MWT, ft $U = 2,446, p < 0.001, d = 0.507$	No Yes	671.7 646.1	630.4 to 718.5 587.9 to 681.6
NIH Balance, theta $U = 2,571, p = 0.003, d = 0.446$	No Yes	0.872 0.559	0.496 to 1.002 0.105 to 0.934
Balance boards, % $U = 2,102, p < 0.001, d = 0.681$	No Yes	0.620 0.498	0.517 to 0.716 0.303 to 0.600

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; T25FW = Timed 25 Foot Walk; 2MWT = 2 Minute Walk Test.

MS and for patients with low disability as measured by EDSS; nearly one-third of our cohort reported a fall or near fall during a 1-month survey period. Furthermore, our fall prevalence of 16.8% is likely an underestimate of overall fall rate because we surveyed falls only in a recent 1-month period to minimize recall bias. These results align with a study of falls that found that younger adults with MS fall more than age-matched persons without MS.¹⁶ Dynamic balance as measured by the balance boards was the best performance predictor of both falls and near falls, and the only performance metric to predict falls and falls/near falls independently of patient report or MS disease burden. This again emphasizes balance dysfunction as a driver of ambulation difficulties in early MS.

Posturography has been used successfully in research to discriminate between patients with MS who fall and those who do not^{13,35–38} and to predict future gait.³⁹ However, in our cohort, a simple behavioral balance task (balance boards) was a good predictor of future falls and near falls. More than half of the fallers with MS were unable to complete 3 error-free tandem walks on the 4.5-in-wide board, and 41.9% of them could not complete even 1 error-free walk on the board. More in-depth investigation is needed into neural correlates of fall risk, but other work has noted an association of recurrent falls with prominent lesion burden in the middle cerebellar peduncle and

brainstem.³⁵ However, while volumetric imaging variables are not routinely assessed in day-to-day clinical practice and widespread application of posturography is limited by cost and time, patient report of walking/physical functioning and a brief higher-challenge balance task can be easily implemented to aid screening of patients at risk for falls and injury. In fact, although we have focused mostly on performance metrics, it is notable that patient-reported walking (MSWS-12) was more related to MRI markers of disease severity than traditional clinical metrics (T25FW, EDSS), and patient-reported physical symptoms at baseline (MSIS-phys) independently predicted future fall risk. These findings highlight the value of the patient's perspective on her/his own function when traditional metrics (e.g., T25FW) appear normal. Such patients can be referred for early balance intervention with the hopes of mitigating future risk.

Persons with MS have an increased risk of injurious falls and fracture compared with age-matched persons without MS^{12,14,15} attributable to a higher fall rate but also to higher rates of comorbid osteoporosis in patients with MS.⁴⁰ More than a quarter of our young cohort (27.2%) reported injurious falls in a 1-year period. Several moderate to severe injuries were reported, including long bone fractures. Fall-related injury can have a profound impact on an individual's overall health and ability to work. Because guidelines exist for managing falls in older adults⁴¹ due to the associated morbidity and mortality, falls and fall-related injury should also be considered a modifiable risk factor for all-cause disability in individuals of all ages with MS.

Our findings highlight the need for more sensitive but clinically feasible longitudinal balance testing for patients with MS. Earlier detection of subtle balance disturbance provides clinicians with an opportunity to offer early rehabilitative intervention for patients at risk for falls and resultant injury. However, the necessity for more sensitive clinical tools extends beyond the neurologist's office. There is an urgent need for updated clinical trial endpoints for testing therapeutic options in MS.⁴² Several therapies have failed to show efficacy on the EDSS or MSFC despite significant effects on disease activity, revealing the limitations of these traditional metrics to detect subtler longitudinal changes in disability.⁴³ Use of easy-to-administer, higher-challenge gait and balance tasks may enhance the ability to detect a meaningful long-term therapeutic impact in the context of clinical trials aiming to prevent decline. These tests, which correlate well with patient self-report and relevant neuroimaging markers, can also be vital additions to trials aimed at therapies for progressive MS, for remyelination strategies, and for symptomatic or rehabilitative therapies. Additional validation studies are needed before novel measures can be used in the clinic or clinical trial setting, including test-retest reliability.

These baseline data provide a framework for understanding gait and balance dysfunction in early MS. Our work has several limitations, including analysis of falls limited to a 1-month period, the low number of patients with fall-related injuries, and the lack of T25FW data for healthy controls to compare

Table 5 Results of logistic regressions predicting risk of future falls

	Step	Predictors retained	Wald (1)	p Value	Odds ratio	95% CI		
						Lower	Upper	
Predicting falls								
Model 1	1	Balance boards	20.640	<0.001	0.007	0.001	0.057	
	2	2MWT	6.955	0.008	0.992	0.986	0.998	
		Balance boards	13.592	<0.001	0.013	0.001	0.130	
Model 2	1	Balance boards	20.640	<0.001	0.007	0.001	0.057	
	2	Balance boards	11.939	<0.0.001	0.017	0.002	0.170	
		MSIS-phys	7.514	0.006	1.040	1.011	1.070	
Model 3	1	Balance boards	18.562	<0.001	0.008	0.001	0.069	
	2	Balance boards	10.700	0.001	0.021	0.002	0.214	
		Thalamus	7.428	0.006	0.708	0.552	0.907	
	3	Balance boards	6.580	0.010	0.041	0.004	0.472	
		Thalamus	5.698	0.017	0.739	0.576	0.947	
		MSIS-phys	5.090	0.024	1.035	1.006	1.066	
Predicting falls and/or near falls								
Model 1	1	Balance boards	19.700	<0.001	0.014	0.002	0.091	
	2	Balance boards	13.098	<0.001	0.023	0.003	0.178	
		EDSS (ref = 0.0)	13.167	0.010				
		1.0	2.764	0.096	0.422	0.153	1.167	
		1.5	0.009	0.926	1.047	0.397	2.757	
		2.0–2.5	4.614	0.032	3.222	1.108	9.369	
		≥3.0	2.007	0.150	2.852	0.686	11.86	
	3	Balance boards	9.263	0.002	0.036	0.004	0.305	
		2MWT	5.309	0.021	0.994	0.989	0.999	
		EDSS (ref = 0.0)	13.895	0.008				
		1.0	3.098	0.078	0.397	0.142	1.111	
		1.5	0.011	0.917	1.054	0.390	2.845	
Model 2		2.0–2.5	5.384	0.020	3.657	1.223	10.935	
		≥3.0	1.341	0.247	2.386	0.548	10.394	
	1	MSIS-phys	23.282	<0.001	1.073	1.043	1.104	
	2	Balance boards	9.913	0.002	0.037	0.005	0.289	
		MSIS-phys	14.931	<0.001	1.061	1.029	1.093	
	Model 3	1	MSIS-phys	22.115	<0.001	1.072	1.041	1.103
		2	MSIS-phys	16.457	<0.001	1.062	1.032	1.094
			Thalamus	14.708	<0.001	0.638	0.507	0.803
		3	Balance boards	4.676	0.031	0.087	0.010	0.796
			MSIS-phys	11.726	<0.001	1.054	1.023	1.086
			Thalamus	10.144	0.001	0.679	0.535	0.862

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; 2MWT = Two-Minute Walk Test; MSIS-phys = Multiple Sclerosis Impact Scale, Physical Subscale.

Model 1 predicted fall outcomes with all performance metrics; model 2 predicted fall outcomes with all performance metrics and measures of patient-reported function; model 3 predicted fall outcomes with all performance metrics, measures of patient-reported function, and neuroimaging variables.

with our MS sample (although T25FW among patients was normatively normal and patients did not differ from healthy controls on a higher-challenge gait endurance task, the 2WMT). A more comprehensive examination of patients in a gait laboratory may be beneficial, especially for detecting subtle differences in gait indicative of poor balance. That said, an important contribution of the current work is the clinical feasibility of the higher-challenge tasks relative to gait laboratory analyses. Note also that we did not assess relapses or disease activity during the year between baseline and fall assessment, which would have been helpful to control for in analyses. That said, our methods reflect the real-life prognostic demands in the clinical setting where knowledge of future relapses is unknown. Lastly, neuroimaging analyses were not designed to identify precise neural mechanisms of gait disturbance and fall risk. Instead, our main reasons for neuroimaging analyses were to determine which performance metrics were most related to MS disease burden generally and to evaluate whether baseline performance metrics independently predicted future fall risk over and above baseline MRI markers of disease. Our planned 3-year longitudinal follow-up will be helpful in better understanding mechanisms for gait impairment and neural correlates of gait change over time; we will be able to examine how changes in disease (e.g., a new cerebellar lesion) relate to changes in gait and balance and how falls relate to longer-term outcomes. Longitudinal analysis will also judge the ability of our higher-challenge tasks to accurately reflect patient-reported change in gait and balance dysfunction over time; to correlate with clinical and radiographic MS disease activity or progression; and to predict future falls, near falls, and injury further into the future.

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Continued

Appendix (continued)

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