Journal of Neurology (2019) 266:3022–3030
https://doi.org/10.1007/s00415-019-09500-z

ORIGINAL COMMUNICATION

Deterioration of specific aspects of gait during the instrumented 6-min walk test among people with multiple sclerosis

S. Shema-Shiratzky[1] · E. Gazit[1] · R. Sun[2] · K. Regev[3] · A. Karni[3,4,5] · J. J. Sosnoff[2] · T. Herman[1] · A. Mirelman[1,4,5] · Jeffrey M. Hausdorff[1,4,6,7]

Received: 24 June 2019 / Revised: 4 August 2019 / Accepted: 6 August 2019 / Published online: 6 September 2019

Abstract

Prolonged walking is typically impaired among people with multiple sclerosis (pwMS), however, it is unclear what the contributing factors are or how to evaluate this deterioration. We aimed to determine which gait features become worse during sustained walking and to examine the clinical correlates of gait fatigability in pwMS. Fifty-eight pwMS performed the 6-min walk test while wearing body-fixed sensors. Multiple gait domains (e.g., pace, rhythm, variability, asymmetry and complexity) were compared across each minute of the test and between mild- and moderate-disability patient groups. Associations between the decline in gait performance (i.e., gait fatigability) and patient-reported gait disability, fatigue and falls were also determined. Cadence, stride time variability, stride regularity, step regularity and gait complexity significantly deteriorated during the test. In contrast, somewhat surprisingly, gait speed and swing time asymmetry did not change. As expected, subjects with moderate disability ($n=24$) walked more poorly in most gait domains compared to the mild-disability group ($n=34$). Interestingly, a group × fatigue interaction effect was observed for cadence and gait complexity; these measures decreased over time in the moderate-disability group, but not in the mild group. Gait fatigability rate was significantly correlated with physical fatigue, gait disability, and fall history. These findings suggest that sustained walking affects specific aspects of gait, which can be used as markers for fatigability in MS. This effect on gait depends on the degree of disability, and may increase fall risk in pwMS. To more fully understand and monitor correlates that reflect everyday walking in pwMS, multiple domains of gait should be quantified.

Keywords Multiple sclerosis · Gait · Fatigability · Fatigue · Fall risk · Walking disability · Wearables · Body-fixed-sensor · Accelerometer

Introduction

Among people with multiple sclerosis (pwMS), the ability to walk safely and independently over long distances often deteriorates as the disease progresses [1], impeding daily functioning [2]. Moreover, patients with relapsing–remitting MS report that gait, balance and fatigue have the largest effect on their quality of life [3]. Indeed, perhaps because of these symptoms, pwMS apparently spend less of the day walking, compared to healthy controls and sustained walking

✉ Jeffrey M. Hausdorff
jhausdor@tlvmc.gov.il

1 Center for the Study of Movement, Cognition and Mobility, Tel Aviv Sourasky Medical Center, 6 Weizmann St., 6423906 Tel Aviv, Israel

2 Motor Control Research Laboratory, Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL, USA

3 Neuroimmunology and Multiple Sclerosis Unit of the Department of Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

4 Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

5 Department of Neurology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

6 Department of Physiotherapy, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

7 Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA

is infrequent during the daily routine [1, 4]. Nonetheless, a complete understanding of the factors that contribute to limitations in daily ambulation and the ability to quantify these gait alterations are lacking.

One attempt at investigating these questions is to use timed tests that measure walking over a relatively long period of time (i.e., minutes instead of seconds). For example, results based on tests of 2 or 6 min walking tasks in the lab showed a higher correlation with real-life mobility (i.e., daily step count, walking speed and total distance) compared to short tests in which gait is evaluated over just a few meters or seconds [4, 5]. In other words, relatively long walking tests have greater ecological validity and may be more relevant measures of functional capacity among pwMS [4]. Moreover, the assessment of prolonged walking apparently reflects the effect of fatigue on physical function [6] and captures gait alterations even in patients with mild disability [7]. Consequently, tests such as the 6-min walk test (6MWT) are commonly employed in the clinical evaluation of pwMS.

The conventional outcome of the 6MWT is the maximal distance a person walks during the timed task. The test was originally proposed to evaluate cardio-respiratory fitness [8] and has since been extended as a valid and reliable method to assess walking endurance in people with a variety of health conditions [7]. However, the performance on the 6MWT depends on more than physical fitness alone. For example, in pwMS, the 6MWT distance was more strongly related to measures of walking performance compared to its association with aerobic and muscular capacity [9]. In addition, cadence and stride length as measured during a short walk explained differences in 6MWT performance between pwMS and healthy controls and by the level of disability within MS [10]. Nonetheless, it is not yet known if quantifying gait performance during the 6MWT would yield similar results, whether different aspects of gait respond similarly during the walking, and whether the evaluation of multiple aspects of gait provide additional information not captured by the 6MWT distance measure alone.

Monitoring gait during the 6MWT offers a unique opportunity to investigate the dynamic changes that occur over the entire walk. For example, recording the distance walked over each 1-min segment of the test revealed that compared to controls, pwMS not only walk slower throughout the test but also show greater deceleration between the first and last segments [7, 11]. In other words, the decline in performance during the test provided an objective measure of fatigability during prolonged walking. Notably, the latter term should be distinguished from the term “fatigue” which refers to the subjective sensation of weariness [12]. Furthermore, the addition of body-fixed sensors to instrument the 6MWT can inform on the dynamics of multiple aspects of gait, and possibly provide additional measures for walking-related fatigue, beyond distance and gait speed. A growing body of literature has demonstrated that different aspects of gait reflect disparate neurological and physiological underpinnings [13]. To date, only a few published reports utilized kinematic [14], kinetic [15] or acceleration-derived measures [16–18] to characterize changes in gait performance across the 6MWT among pwMS. Nonetheless, it is still unclear which aspects of gait vary during prolonged walking, which gait features are sensitive to fatigability in pwMS, and whether or not these relationships depend on the level of MS disability. To address these gaps, the aims of the present study were to determine which gait features deteriorate over the course of the 6MWT and to examine whether these changes are related to disability level, fatigue, and other clinical characteristics among pwMS.

Materials and methods

Participants

Fifty-eight patients with relapsing–remitting MS participated in this cross-sectional analysis. Subjects were recruited as part of a multi-center intervention study aimed to enhance gait, cognition, and motor–cognitive interactions in MS. The data utilized in the analysis were collected during the participants’ first visit prior to the intervention at the Tel Aviv Sourasky Medical Center (TASMC) in Israel and in the University of Illinois Urbana-Champaign (UIUC) in Urbana, IL, USA. The sample included patients aged 18–65 years who were free from a relapse in the past 30 days. All subjects were ambulatory with mild to moderate disability as determined by an Expanded Disability Status Scale (EDSS) score of 2–6. Individuals with other neurological, orthopedic or rheumatic pathology that may affect gait were excluded. The study was approved by the local institutional review boards at TASMC and UIUC. All subjects provided informed written consent prior to participation.

Procedures

Subjects performed the 6MWT overground walking back and forth in a well-lit corridor free of obstacles and other people, according to the American Thoracic Society guidelines [19]. Briefly, after a seated rest of at least 15 min, participants were asked to cover the maximal distance during 6 min, with no specific instructions regarding gait speed or specific encouragement during the test itself. The use of an assistive device and short resting breaks (i.e., while standing) were permitted as needed. A research assistant walked beside the participants to assure safety and informed them of the time elapsed after completing each minute of the task.

Demographic and clinical data were collected using structured questionnaires. The Modified Fatigue Impact Scale

(MFIS) was used to assess the subjective burden of fatigue on physical, cognitive and psychosocial functions [20]. The subject's perceived MS-induced gait disability was evaluated using the 12-Item MS Walking Scale (MSWS-12) [21]. In addition, participants reported the number of falls that they experienced in the past year.

Gait data collection and processing

Spatial–temporal features of gait during the 6MWT were captured using a set of sensors worn on the lower back and ankles (Opal, APDM). The sensors include a 3D accelerometer and a 3D gyroscope that are sampled at a 128 Hz. To assess gait changes across the 6MWT, we used previously validated algorithms [22, 23] to extract gait parameters that reflect the steady-state walking in each minute of the test. First, we divided the raw signal into 1-min segments and excluded turning motion (as evidenced from the yaw signal of the gyroscope). Then, seven features were extracted from each 1-min segment to represent different gait domains that are considered independent from one another, following the suggestion of Lord et al. [13]. The features included gait speed (representing the "pace" domain), cadence ("rhythm" domain), stride time variability and stride regularity ("variability" domain), step regularity and swing time asymmetry ("asymmetry" domain), and sample entropy ("complexity" domain). To avoid redundancy, we did not present parameters that demonstrated similar results within the same domain. For example, we did not include step length since it was so closely related to gait speed. This approach for gait analysis has been previously applied in healthy older adults, patients with Parkinson's disease and idiopathic fallers [22–25].

Stride time variability refers to the ratio between the standard deviation and the mean of the stride time series, expressed as a %, and therefore represents the variability domain of the gait cycle timing. Higher gait variability was related to deterioration of mobility in many cohorts and in pwMS [22, 25, 26]. The step regularity and stride regularity parameters are index scores that range between 0 and 1 and determine the consistency in the acceleration waveform, using an unbiased autocorrelation [27, 28]. While stride regularity is representative of the variability domain, the step regularity measure reflects the asymmetry domain as it compares the acceleration signals between the left and right feet. Lower regularity scores suggest an inconsistent gait pattern and are reported in patients with Parkinson's disease, older adults and people with an asymmetrical gait that results from stroke, osteoarthritis or amputation [28–30]. To quantify swing time asymmetry, we determined which foot had the shorter and longer mean swing time (SSWT and LSWT respectively) and used the following formula $100 \times |\ln(\mathrm{SSWT}/\mathrm{LSWT})|$ [31], in which higher values reflect a greater degree of gait asymmetry. Sample entropy of the gait signal was used to describe the domain of gait complexity [32] wherein lower values indicate a less complex gait pattern, often related to aging, pathology, and increased fall risk [33].

Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics version 25. The cohort was stratified into a mild-disability group (EDSS 2–3.5) and a moderate-disability group (EDSS 4–6). Demographics and clinical characteristics were compared between groups using independent-samples *t* tests for continuous variables with a normal distribution, Mann–Whitney for ordinal variables (i.e., EDSS scores), and Pearson's Chi-square for dichotomous variables (i.e., gender). Repeated measures ANOVA was performed on each gait feature to assess the effects of fatigue (within-subject, 6 levels corresponding to each 1 min period during the 6MWT), group (between-subject, 2 levels, i.e., mild vs moderate disability) and group × fatigue interaction. To further explore the changes induced by fatigue, we conducted pairwise comparisons of performance between minutes for the entire cohort and within each group. The Bonferroni method was used to correct for these multiple comparisons. Gait variables that were not normally distributed were transformed using $\mathrm{Log10}(x)$ (i.e., stride time variability and gait asymmetry), or $(x)^2$ (i.e., step regularity) function, to achieve normal distributions before applying the RMANOVA analyses. To address our second aim, we examined the association between the degree of change in gait features and the subject's report of perceived fatigue, gait disability, and fall history using Spearman's ρ. For this purpose, the magnitude of change in each gait feature during the 6MWT was determined as the difference between the maximal and minimal values measured across the 6 min and served as a measure of fatigability.

Results

Participant characteristics

Based on the EDSS scores, 34 subjects were included in the mild-disability group and 24 subjects were included in the moderate-disability group. Participants in the two groups were similar with respect to age, gender, height, weight and disease duration ($p > 0.08$, see Table 1). As expected, subjects with moderate disability scored significantly higher (i.e., reported having worse walking ability) on the MSWS-12 questionnaire, compared to the participants with mild disability ($p < 0.001$). In addition, pwMS with moderate disability reported a higher burden of physical and psychosocial

Table 1 Demographics and clinical characteristics of subjects in the two disability groups

	Mild disability ($n=34$)	Moderate disability ($n=24$)	p value
Age (years)	49.0 (11.2)	48.9 (8.0)	0.955
Gender (male/female)	11/23	6/18	0.545
Height (cm)	169.6 (9.2)	166.8 (8.4)	0.244
Weight (kg)	78.9 (16.5)	70.6 (18.2)	0.080
Disease duration (years)	13.8 (10.9)	13.6 (7.5)	0.859
Expanded Disability Status Scale (EDSS)	2.5 [2, 3]	5.25 [4–6]	**<0.001**
History of falls in the past year	1 [0–3]	2 [0–5]	0.133
Distance walked during the 6-min walk test (m)	434.6 (80.4)	291.0 (102.3)	**<0.001**
Multiple sclerosis walking scale-12	48.8 (22.7)	78.7 (15.2)	**<0.001**
Modified fatigue impact scale-total	36.3 (20.1)	46.7 (14.2)	0.065
Physical subscale	17.2 (9.6)	22.9 (7.0)	**0.036**
Cognitive subscale	16.1 (9.9)	19.5 (7.2)	0.226
Psychosocial subscale	3.0 (2.3)	4.4 (2.1)	**0.044**

Entries are presented as mean (standard deviation) for continuous measures. Ordinal measures and parameters that were not normally distributed are presented as median [inter-quartile range]

Measures that significantly differed between the two groups appear in boldface

fatigue ($p<0.044$), while cognitive fatigue did not differ ($p=0.226$) between the two groups. Similarly, the number of falls in the past year was comparable between the mild- and moderate-disability groups ($p=0.133$). Participants with mild disability covered a mean distance of 434.6 ± 80.4 m during the 6MWT, while the moderate-disability group walked a mean of 291.0 ± 102.3 m ($p<0.001$).

Changes in gait across the 6MWT

Table 2 summarizes the changes in the gait features that were observed during each minute of the 6MWT in the two disability groups and presents the main effects of fatigue, group and group × fatigue interaction. The moderate-disability group walked slower than the mild group ($p<0.003$), with a lower cadence, lower (i.e., worse) step regularity, and lower stride regularity, and higher (i.e., poorer) stride time variability (see Table 2). In addition, sample entropy, a measure of gait complexity, was significantly higher in the mild-disability group ($p=0.038$). There was a significant main effect of fatigue for cadence, sample entropy, stride time variability, step regularity, and stride regularity ($p<0.016$). Generally, gait performance was best during the 1st minute of the test. Deterioration of gait variability (i.e., stride time variability and stride regularity) occurred during the minute 5 of the walk, while gait asymmetry (i.e., step regularity) became significantly worse in the last minute of the test. Interestingly, gait speed and swing time asymmetry did not change across the 6 min in both groups.

Figure 1 illustrates the minute-to-minute changes in gait rhythm (i.e., cadence) and gait complexity (i.e., sample entropy) during the 6MWT among the two disability groups. A significant group × fatigue interaction effect was observed for cadence ($p=0.02$) and for sample entropy ($p=0.017$); the mild-disability group maintained a constant rhythm and complexity pattern during the entire test, whereas cadence and sample entropy significantly decreased in the moderate-disability group across the 6MWT, starting from the 2nd minute of the walk onwards (see also Table 2).

Correlations between walking fatigability and clinical features

The relationships between observed gait changes during the 6MWT and self-reported clinical measures are presented in Fig. 2. Worse gait disability, reflected by higher MSWS-12 scores, was significantly correlated with greater changes in the variability and asymmetry domains of gait (i.e., with stride time variability, stride regularity, step regularity, and swing time asymmetry, $\rho>0.428$, $p<0.007$), and with shorter distance walked during the test ($\rho=-0.670$, $p<0.0001$). In addition, a higher burden of fatigue was associated with larger changes in step regularity and stride regularity. The gait regularity features were correlated with worse physical fatigue ($\rho>0.495$, $p<0.001$) and, to a lesser extent, with psychosocial fatigue ($\rho>0.365$, $p<0.011$), but were unrelated to cognitive fatigue. Interestingly, while gait speed changes during the 6MWT were not associated with fall history or distance walking, changes in swing time asymmetry during the 6MWT were most closely associated with important functional measures: fall history ($\rho=0.330$, $p=0.035$), gait disability ($\rho=0.463$, $p=0.003$) and distance walked ($\rho=-0.592$, $p<0.001$).

Table 2 Minute-to-minute changes in gait performance in the two disability groups

Gait domain and feature	Disability group	Performance per minute						RMANOVA p values		
		Min 1	Min 2	Min 3	Min 4	Min 5	Min 6	Fatigue effect	Group effect	Group × fatigue effect
Pace domain Gait speed [m/s]	Mild	1.40 (0.28)	1.43 (0.27)	1.42 (0.31)	1.43 (0.30)	1.43 (0.30)	1.44 (0.32)	0.716	**0.003**	0.567
	Moderate	0.99 (0.31)	0.98 (0.34)	0.95 (0.33)	0.95 (0.31)	0.97 (0.36)	0.93 (0.35)			
	All	1.23 (0.35)	1.25 (0.37)	1.23 (0.39)	1.23 (0.38)	1.24 (0.39)	1.23 (0.41)			
Rhythm domain Cadence [steps/min]	Mild	114.8 (13.1)	113.9 (13.8)	113.4 (14.4)	113.5 (14.8)	112.5 (15.5)	113.2 (15.6)	**< 0.001**	**< 0.001**	**0.020**
	Moderate	99.2 (18.2)	**97.4 (17.8)**[a]	**95.4 (18.5)**[a,b]	**94.5 (18.5)**[a,b]	**93.9 (19.8)**[a]	**94.3 (19.3)**[a]			
	All	108.3 (17.1)	**107.1 (17.5)**[a]	**105.9 (18.4)**[a]	**105.7 (18.9)**[a]	**104.8 (19.6)**[a]	**105.4 (19.5)**[a]			
Variability domain Stride time variability [%]	Mild	3.65 (1.72)	3.20 (1.94)	3.99 (2.50)	3.99 (2.50)	3.95 (2.24)	4.35 (2.89)	**0.016**	**0.002**	0.095
	Moderate	4.68 (2.45)	5.70 (3.30)	5.70 (2.87)	5.85 (2.75)	7.11 (4.41)	5.80 (2.96)			
	All	4.07 (2.10)	4.23 (2.84)	4.69 (2.76)	4.76 (2.73)	**5.25 (3.63)**[a]	4.95 (2.98)			
Variability domain Stride regularity [−]	Mild	0.78 (0.10)	0.79 (0.10)	0.79 (0.10)	0.78 (0.12)	0.78 (0.10)	0.76 (0.13)	**< 0.001**	**< 0.001**	0.110
	Moderate	0.59 (0.20)	0.57 (0.20)	0.57 (0.21)	0.53 (0.19)	**0.54 (0.21)**[a]	0.54 (0.19)			
	All	0.70 (0.18)	0.70 (0.18)	0.70 (0.19)	0.67 (0.20)	0.68 (0.19)	0.67 (0.19)			
Symmetry domain Step regularity [−]	Mild	0.77 (0.13)	0.77 (0.13)	0.75 (0.14)	0.75 (0.15)	0.76 (0.14)	0.74 (0.15)	**< 0.001**	**< 0.001**	0.334
	Moderate	0.53 (0.21)	0.53 (0.21)	0.53 (0.22)	0.50 (0.21)	0.50 (0.20)	0.50 (0.20)			
	All	0.67 (0.20)	0.67 (0.21)	0.66 (0.21)	0.65 (0.22)	0.65 (0.21)	**0.64 (0.21)**[a]			
Symmetry domain Swing time asymmetry [−]	Mild	4.86 (4.99)	4.79 (4.97)	4.72 (4.91)	4.49 (5.01)	4.81 (4.98)	4.67 (5.00)	0.679	0.09	0.315
	Moderate	9.36 (10.93)	9.31 (10.93)	9.77 (10.90)	9.70 (10.83)	9.47 (10.98)	10.22 (11.54)			
	All	6.77 (8.27)	6.71 (8.28)	6.87 (8.31)	6.71 (8.33)	6.79 (8.32)	7.03 (8.77)			
Complexity domain Sample entropy [−]	Mild	1.92 (0.43)	1.92 (0.44)	1.91 (0.47)	1.93 (0.47)	1.94 (0.47)	1.97 (0.50)	**0.007**	**0.038**	**0.017**
	Moderate	1.73 (0.47)	**1.67 (0.47)**[a]	**1.65 (0.46)**[a]	**1.64 (0.47)**[a]	1.65 (0.50)	1.68 (0.46)			
	All	1.83 (0.45)	1.82 (0.47)	**1.80 (0.48)**[a]	1.81 (0.49)	1.82 (0.48)	**1.85 (0.50)**[c]			

The average performance per minute is presented as mean (standard deviation). Stride time variability, step regularity and swing time asymmetry were transformed using the Log10(x) or the $(x)^2$ function to achieve normal distribution and qualify for the RMANOVA analyses. The p values of the RMANOVA were corrected using the Greenhouse–Geisser method due to violation of the sphericity assumption

Significant effects of the RMANOVA are presented in boldface

[a]Denotes significant change in performance as compared to minute 1 of the walk

[b]Presents significant change compared to minute 2

[c]Marks a significant change from minute 3, after correction for multiple comparisons

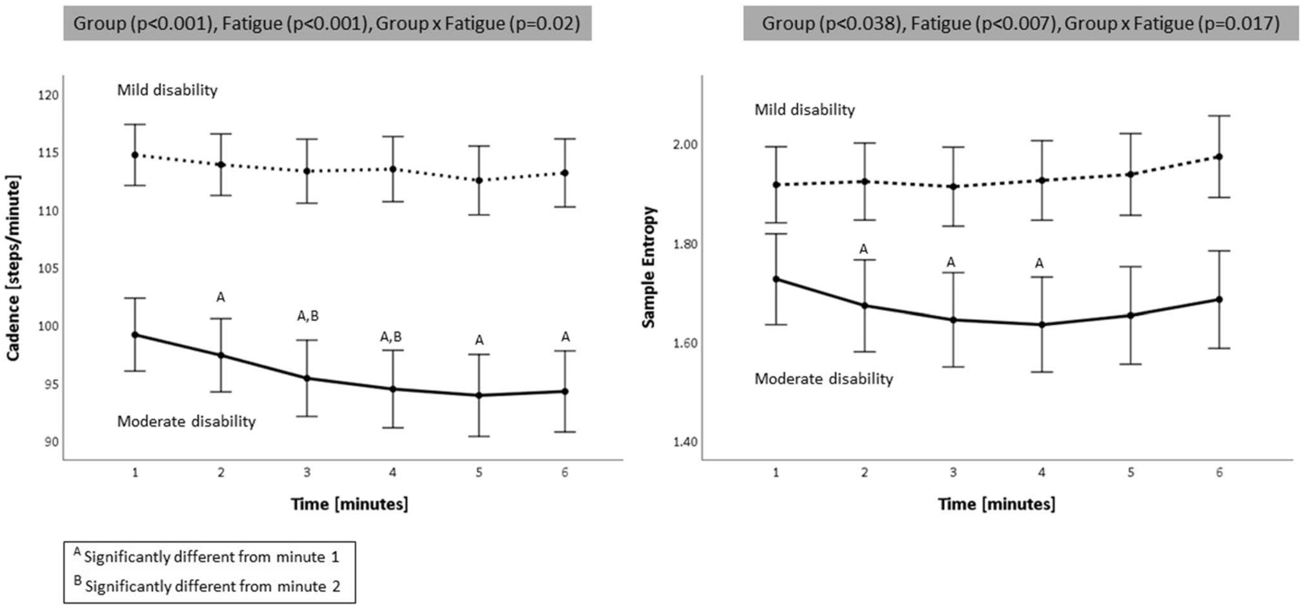

Fig. 1 Changes in cadence and sample entropy (complexity) across the 6MWT in the mild- and moderate-disability groups. Note that a significant effect of fatigue, group and group × fatigue interaction was observed, indicating that the changes during sustained walking are different in the two disability groups. Significant changes within each group are denoted with A for a decline compared to the 1st minute of the test and B for a decline from the 2nd minute of the walk (adjusted for multiple comparisons)

Rate of walking fatigability	Self-reported clinical measures: Fatigue: total	Fatigue: physical	Fatigue: cognitive	Fatigue: social	Gait disability	Fall history	Distance
Decline in speed	-0.232	-0.178	-0.259	-0.173	-0.080	-0.094	0.180
Decline in cadence	-0.094	0.051	-0.224	0.103	0.187	0.131	-0.200
Increase in stride time variability	0.207	0.301	0.068	0.141	0.428**	0.293	-0.282
Decline in stride regularity	0.289*	0.495**	0.059	0.365*	0.509**	0.133	-0.427**
Decline in step regularity	0.342*	0.508**	0.161	0.380**	0.513**	0.136	-0.207
Increase in swing time asymmetry	0.052	0.143	-0.071	0.098	0.463**	0.330*	-0.592**
Decline in sample entropy	-0.053	-0.025	-0.075	0.043	-0.004	0.028	0.107

* p<0.05 **p<0.01

-1.0 0.0 1.0

Fig. 2 Heat map summarizing the correlations between the clinical aspects of MS and the observed changes in gait across the 6MWT. The color scheme is used to characterize the type of association between the measures. Dark red denotes negative high association, whereas dark green indicates a positive high association. Significant correlations are marked with an asterisk. The magnitude of change for each gait parameter was calculated as the difference between maximal and minimal values, measured during the 6MWT. Note that gait speed changes were not strongly associated with distance walked or fall history, while change in gait asymmetry were. 6MWT: 6-min walk test

Discussion

The present study provides a relatively detailed and novel view of the deterioration of gait during prolonged walking in pwMS, beyond the measures of total distance and gait speed. Our findings reveal that, as expected, poor gait performance is related to higher disability level in MS. Interestingly, however, only specific aspects of gait significantly changed across the 6MWT, leading to exacerbation of the gait disturbance as walking persisted. Moreover, subjects with mild and moderate disability demonstrated distinct patterns of deterioration in cadence and complexity. The decline in gait performance during the 6MWT was correlated with patient-reported clinical measures of fatigue, gait disability, and falls. These findings indicate that all measures of gait do not respond similarly to sustained walking and that the response depends on the level of disability. More generally, the present findings demonstrate that quantifying the 6MWT provides a more complete, quantitative characterization of gait that enhances our understanding of walking fatigability in MS.

Gait alterations measured during the 6MWT

Our findings that multiple aspects of gait deteriorate during the 6MWT are consistent with evidence from several previous studies. Engelhard et al. [16] applied a dynamic time wrapping method to inertial gait data in healthy controls and pwMS who performed the 6MWT. They found progressive changes between gait cycles in MS subjects with mild to moderate disability (i.e., EDSS 0–4.5), but not in controls or pwMS with severe disability (EDSS 5–6.5). While the dynamic time wrapping measures indicate general inconsistency across time in gait performance, the precise nature and direction of this change remain unclear. In contrast, the metrics that we used in the current study enable us to better characterize the changes observed in gait over time. We found that step regularity and stride regularity were significantly reduced across the test. This implies that fatigability in pwMS may trigger or exacerbate gait asymmetry and walking instability [29, 34]. In addition, the participants in the present study increased their stride time variability during the test, which further indicates worsening of gait inconsistency and the neural control of walking. Similarly, Qureshi et al. found that the gait cycle duration variability (i.e., temporal variability) increased during the 6MWT, specifically in pwMS who had worse fatigue (MFIS > 42) and more severe gait disability (MSWS-12 > 36) [18]. Taken together, the changes that we detected during the 6MWT suggest that gait fatigability in pwMS may exaggerate fall risk during prolonged walking; recall also Fig. 2. This observation may explain in part the high risk of falls in pwMS and the association between fatigue and falls in pwMS [35] and perhaps help elucidate why sustained walking is less frequent during community ambulation in these patients compared to healthy controls [36].

Cadence is another gait feature that significantly changed during the 6MWT in the present study. Two previous reports on cadence shifts during the 6MWT were inconclusive. Consistent with the current findings, in a pilot study that involved 15 pwMS with moderate disability (EDSS 4–6), cadence was significantly reduced between the first and last ten gait cycles during the 6MWT [14]. In contrast, Motl et al. [17] did not detect changes in cadence during the 6MWT among 95 pwMS with disability ranging between mild (EDSS 2–3.5), moderate (EDSS 4–5.5) and severe (EDSS 6–6.5). The authors concluded that the step rate (i.e., cadence) does not change over the 6MWT in persons with MS and speculated that other gait features, e.g., step length, are reduced from minute to minute during the test. The discrepancies between the former investigation and our findings may be related to several factors. First, there were different disability clustering methods between the studies. A simple contrast of walking distance revealed that the corresponding disability groups across the studies performed differently on the 6MWT. Second, Motl et al. used a modified version of the 6MWT protocol in which fast gait speed is emphasized and rests are not permitted during the test [7]. It is possible that these modifications restricted the participants in the earlier study from altering their step rhythm (i.e., cadence) and maybe even led to the decreased in gait speed observed in other studies using this modified protocol [7]. The participants in the current study maintained gait speed throughout the test, possibly at the expense of other gait variables. Thus, further examination in larger and diverse cohorts, perhaps comparing between the conventional and modified 6MWT protocols are needed to better establish how cadence and other gait domains change during sustained walking in MS.

Interestingly, we found that subjects with moderate disability decreased their number of steps from minute to minute, while cadence in pwMS with mild disability was preserved throughout the walk. A similar group × fatigue interaction effect was found for sample entropy. Among the subjects with mild disability, sample entropy did not change from one minute to the next during the 6MWT. In contrast, in pwMS and moderate disability, sample entropy significantly decreased in minutes 2, 3 and 4 of the test, as compared to the 1st minute, and seemed to return toward the initial values during the final 2 min of the test (recall Fig. 1), however, these later changes were not statistically significant. Interestingly, gait speed and other measures did not show these types of changes during the 6MWT.

Sample entropy measures the complexity of the gait acceleration signal. Previous work indicated that loss of complexity is related to functional decline in older adults and represents loss of adaptability of daily life walking [33]. In addition, lower sample entropy was found in adults with symptomatic knee osteoarthritis and in people with Parkinson's disease, as compared to healthy controls [37, 38]. In the present study, we found that sample entropy was lower among subjects with worse disability, and that it further decreased during the 6MWT, marking a decline in performance specifically in the moderate-disability group. Cadence and entropy appeared to be sensitive gait markers to detect fatigability during the relatively prolonged task, and moreover, indicate disparate behaviors related to disability in MS. These findings suggest that fatigability is manifested differently in pwMS who vary in disability levels. On a practical, clinical level, this suggests that the assessment of fatigability and interventions to alleviate fatigability should be adapted to disability status among pwMS.

Correlation between gait fatigability and clinical outcomes

The association between the perception of fatigue (e.g., measured with the MFIS) and the expression of fatigue during the performance of a task is complex and is often considered difficult to establish [12]. In a recent meta-analysis, Loy et al. found a moderate, positive correlation between fatigue and fatigability ($r = 0.31$) in pwMS [39], taking into account measures of gait performance and muscle strength tasks. In the current study, we observed even stronger associations (i.e., $\rho > 0.495$) between the physical fatigue subscale of the MFIS with fatigability measured via the step regularity and stride regularity (recall Fig. 2). Moreover, the correlation between the distance measure and physical fatigue was lower, emphasizing the importance and the added value of using sensor-based measures in the evaluation of locomotion in MS. Consistent with the literature, we also found strong correlations between several measures of fatigability and gait disability as measured by the MSWS-12 [16, 18], which further supports the clinical relevance of the gait features used in this investigation.

Conclusions and limitations

This study has several limitations. First, our sample was relatively small and it is possible that an examination of a larger cohort would yield additional, more subtle group differences and group × fatigue interactions. Second, we did not have a control group; this precludes the comparison to the possible changes that occur in healthy individuals during the 6MWT. Nonetheless, the participants in this study were relatively diverse in terms of age, disability status, and disease duration and may serve as an adequate representation of a spectrum of ambulatory patients with relapsing–remitting MS. Another strength of the study is the report on multiple, independent domains of gait that expand the understanding of the dynamic changes in locomotion among pwMS. The method used in the present work opens the possibility to better assess disability and to more fully understand the effects of fatigue on walking, other daily-living activities, and fall risk. From a clinical perspective, the findings highlight the importance of dynamic assessment throughout sustained walking like that which occurs during the 6 min walking test. In the future, these gait metrics can potentially be used as sensitive markers to evaluate response to medical treatment or other interventions, and perhaps even shed light on the rate of disease progression and prognosis, potentially augmenting the timed 25 foot walk and other tests based on short walking bouts [40]. Future studies are needed to evaluate how changes over time during sustained walking respond to interventions in pwMS. The present findings motivate and set the stage for those prospective investigations and suggest that the ability to track and monitor fatigability and other MS symptoms may be enhanced by evaluating changes in multiple gait features during sustained walking.

Acknowledgments We thank the study participants for their time and contribution to this research. This work was supported in part by a Grant for the National Multiple Sclerosis Society (RG-1507-05433).

Compliance with ethical standards

Conflicts of interest All authors declare that they have no conflict of interest.

Ethical approval This study was conducted in accordance with the standards and approved by local human study committees, and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects provided informed written consent prior to their inclusion in the study.

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