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BALISTIERI SANTINELLI, Felipe; ABASIYANIK, Zuhal; RAMARI FERREIRA, Cintia; GYSEMBERG, Griet; KOS, Daphne; Pau, Massimiliano; Kalron, Alon; MEYNS, Pieter; Ozakbas, Serkan & FEYS, Peter (2024) Manifestations of walking fatigability in people with multiple sclerosis based on gait quality and distance walked during the six minutes walking test. In: Multiple Sclerosis and Related Disorders, 91 (Art N° 105909).

DOI: 10.1016/j.msard.2024.105909
Handle: http://hdl.handle.net/1942/44559

Title: Manifestations of walking fatigability in people with multiple sclerosis based on gait quality and distance walked during the six minutes walking test

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Abstract

Background: Distance walking fatigability (DWF) in people with multiple sclerosis (pwMS) is defined as a decrease in the distance walking over time. However, declines in gait quality (i.e., gait quality fatigability- GQF) may occur independently or alongside DWF.

Objective: i) to investigate how walking fatigability manifests and its prevalence in pwMS; ii) to describe the temporal pattern of the changes of specific gait characteristics during the 6-minute walking test (6MWT)

Methods: Eighty-eight pwMS (EDSS 4[0-6.5], 49[21-70] years) and 47 healthy controls (HC- 46[25-60] years) performed the 6MWT wearing inertial measurement units. Gait characteristics (stride length, sensor-based gait speed, cadence, double support, step duration, stance phase, step duration asymmetry, step duration variability, foot-strike, toe-off, and leg circumduction) and walking distance were recorded in 1-minute intervals. A fatigability index was calculated by comparing the last and first minute of the 6MWT to identify abnormal worsening based on cutoff scores. The manifestation of walking fatigability was counted. The temporal pattern of worsening of gait characteristics during the 6MWT was examined in pwMS exceeding the cutoff values, compared to pwMS without abnormal changes and HC, using a two-way ANOVA (group vs. minutes)

Results: Thirty-five pwMS presented both DWF and GQF, 2 presented isolated DWF, 27 presented isolated GQF, and 24 presented non-walking fatigability. PwMS having GQF presented worsening in gait characteristics (cadence, step duration, step duration variability, or toe-off angle) from minute 2 onwards of the 6MWT, while HCs and pwMS without abnormal changes stabilized gait from minute 2 towards the end of the 6MWT.

Conclusion: Walking fatigability in pwMS manifests not only as a decrease in walking distance but also as changes in gait quality. Understanding changes in gait characteristics during walking can help tailor rehabilitation interventions.

Keywords: Multiple sclerosis; walking fatigability; gait analysis; fatigue; gait quality

Introduction

People with Multiple Sclerosis (pwMS) often have difficulties in maintaining walking performance during prolonged periods, which one can label as walking fatigability. Previous research has defined walking fatigability in pwMS at the activity level of the International Classification of Functioning, Disability, and Health (ICF)(1-3), named distance walking fatigability (DWF) (3). DWF is identified during the 6-minute walking test (6MWT) (4) and is defined as a decrease of at least 10% in the distance walked (i.e., using the distance walked index- DWI) comparing the last with the first minute of the 6MWT (1-3). DWF affects up to 43% of pwMS overall (1, 3) and 51% of cognitively impaired progressive pwMS (5). Its prevalence and severity impact those with more disability, lower walking speed, and progressive phenotype (3). However, the current definition of walking fatigability does not encompass the body function level of the ICF (i.e., gait characteristics and pattern).

Previous studies showed conflicting results concerning changes in gait characteristics during the 6MWT in pwMS. Towards the end of the 6MWT, pwMS became more unstable(6), presenting with uncoordinated and asymmetric gait(7), with higher gait variability(8, 9), drop foot(10), and worsening of step duration and cadence(8, 11). In contrast, others found that balance(12), gait variability(13), and step length or double support(8, 14) remained unchanged. Regardless, there is a lack of studies considering various gait domains (e.g., rhythm, pace, variability) and gait characteristics over time to identify manifestations of walking fatigability at the body function level concomitantly with the activity level. To determine whether changes in gait characteristics are abnormal and, thus, reflect changes in gait quality, reference values during the 6MWT are required. We have previously provided evidence on the test-retest reliability of gait characteristics, minute-by-minute during the 6MWT, and their respective changes (i.e., applying a fatigability index) during the 6MWT(15). We also provided reference values to define when a change is abnormal. These abnormal changes in the gait characteristics (i.e., ICF body function level) during the 6MWT can be defined as gait quality fatigability (GQF). Based on the previous definition of movement quality(16), we define gait quality as the ability of the individual to perform gait optimally (i.e., with a smooth, coordinated gait).

Previous research has demonstrated two distinct patterns of distance walked trajectory over the 6MWT: a more stable performance since minute 1 and a steady decline from minute 2 onwards(17). We have previously reported that by grouping pwMS according to DWF and using the DWI, similar dynamics of the distance walked minute by minute are observed (i.e., pwMS with DWF present a steady decline over the 6MWT)(3). Per our knowledge, no previous study examined the gait characteristics, minute by minute, throughout the 6MWT by grouping pwMS by (non)presenting abnormal changes, using established cutoff scores(2, 15) in the respective gait characteristics. Unveiling the different manifestations of walking fatigability will help to identify the potential underlying causes, such as lack of neural resources, muscle fatigue, and pace strategy. Moreover, the findings of this research might lead to more accurate assessment methods, improved prognosis models, and tailored rehabilitation programs to improve walking fatigability in pwMS.

Therefore, the study aims are twofold: firstly, to investigate how walking fatigability manifests and its prevalence in pwMS, not only in the activity level (i.e., distance walked- DWF) but also in the body function level (i.e., changes in gait characteristics- GQF) by applying determined cut-off scores using a fatigability index(2, 15). We hypothesized that walking fatigability will manifest more often when combined as DWF and GQF than when isolated. Secondly, we investigated the temporal development of changes in gait characteristics minute by minute by comparing pwMS (not) presenting abnormal changes at the last minute and with healthy controls (HC). We expect pwMS with GQF to present a steady decline in performance throughout the 6MWT(3, 18).

Methods

Experimental procedure

This is a cross-sectional exploratory study and a secondary analysis of studies published elsewhere (15, 19). For the full description of the study, please refer to Santinelli et al.,(15) and Abasiyanik et al., (19). The participants were informed about the study procedure and objectives and provided consent by signing an informed consent (approved by the local ethical committees-#B1152021000009, 2021/14-38, Clinical Trials: NCT05412043). After, anthropometric characteristics and clinical evaluation were obtained (see below). Lastly, the participants performed the 6MWT while wearing inertial measurement units (IMUs) to measure the DWF and GQF.

Participants

One-hundred and thirty-five (88 pwMS and 47 HC) participants were included in this study, meeting the following criteria: able to walk for 6 minutes without resting, age between 30 and 70, and ability to comprehend the study instructions. Exclusion criteria included the presence of pregnancy and musculoskeletal or cardiovascular disease interfering with walking (for both groups). Specifically for pwMS, MS diagnosis according to the revised McDonald criteria(20) and Expanded Disability Status Scale (EDSS) scores between 0 and 6.5 were adopted. Participants were recruited from the Belgian MS rehabilitation centres in Melsbroek (NMSC), Overpelt (Noorderhart RMSC), flyers, website, social media of the REVAL research center at UHasselt, the Flemish MS Society and Dokuz Eylul University (Izmir, Turkey).

Descriptive and clinical outcomes

The following tests and questionnaires described participants: i) Cognitive function: Symbol Digit Modality Test (SDMT)(21), ii) Perceived fatigue: Modified Fatigue Impact Scale (MFIS)(22) iii) Perceived walking ability: MS Walking Scale (MSWS-12)(23) and iv) walking capacity: 25-foot walking test (T25FW).

Six-minute walk test

The participants were instructed to walk as fast and safely as possible (using their assistive devices if needed), back and forth along a straight trajectory, across a hallway with cones delimiting the trajectory to be walked (24). Given logistic and space availability through the centers, the 6MWT was performed in corridors lengths of 20, 25, and 30 meters. No encouragement was given throughout the test, and participants were informed about every minute. The distance (meter) was recorded at every minute. To identify DWF, the DWI(1) was calculated according to the formula:

$$Distance\ walking\ index\ (DWI) = \left(\frac{(Distance\ walked\ minute\ n - Distance\ walked\ minute\ 1)}{Distance\ walked\ minute\ 1}\right) * 100$$

Gait quality measurement and data analysis

Three IMUs (Opal, APDM Inc., USA) were set at 128 Hz and placed on the feet and lower back (L4 vertebrae). Gait characteristics were extracted on a gait cycle base and segmented on a 1-minute window (MATLAB). Gait characteristics were averaged within each minute and used as outcomes. The following gait characteristics based on our previous study(15), were reported: i) Pace: Stride length (meters) and gait speed (m/s); ii) Rhythm: cadence (steps per minute), double support (percentage of the gait cycle), step duration (seconds) and stance phase (percentage of the gait cycle); iii) Asymmetry: asymmetry of step duration (absolute difference between left/right legs); iv) Variability: variability of step duration, calculated employing the coefficient of variation; v) Kinematics: foot strike and toe-off

angle and leg circumduction (centimeters). The IMUs calculated the gait characteristics only in the straight line and excluded the acceleration/deceleration phase.

We identify those with GQF using a fatigability index formula (similar to the DWI(1)) applied to each gait characteristic by comparing minute 6 with minute 1. The following cut-off scores were used based on previous publication and reliability(15): stride length (cut-off -11.17%), sensor-based gait speed (cut-off -12.04%), cadence (cut-off -5.24%), double support (cut-off 18.97%), step duration (cut-off 5.34%), stance phase (cut-off 2.74%), step duration asymmetry (cut-off 66.89%), step duration variability (cut-off 31.02%), foot-strike (cut-off -22.42%), toe-off (cut-off -4.05%), and leg circumduction (cut-off 35.7%). To avoid redundancy, the same index was applied for only a few variables to define the magnitude of change every minute(13).

Statistical analyses

Statistical analyses were conducted with R Studio (V. RStudio 2023.03.0+386 for Windows) and SPSS (29.0.0.0(241)). The $p<0.05$ was adopted to indicate a significant difference. PwMS were grouped in accord with the different walking fatigability manifestations as follows: i) DWF: only presenting abnormal changes in DWI; ii) GQF- presenting abnormal changes in one or more gait characteristics; iii) DWF/GQF: the combination of the presence of at least abnormalities in DWI and in one gait characteristic and; iv) non-walking fatigability (NWF): no abnormal changes in DWI or any gait characteristics. Groups (pwMS vs. HC and DWF vs. DWF/GQF vs. GQF vs. NWF) were compared for anthropometric and descriptive outcomes with one-way ANOVA (normally distributed variables and) Pearson's Chi-square (dichotomous variables), and Kruskal-Wallis (non-normal variables) test. Post-hoc with a Bonferroni correction for multiple comparisons were applied where applicable.

A frequency analysis was performed in order to identify the distribution among pwMS presenting DWF/GQF, DWF, GQF, or NWF. Individual cases for each gait characteristic were represented as a heatmap plot to achieve this. Additionally, two bar plots were made: i) showing the frequencies of the different walking fatigability manifestations *at aggregated level* and ii) the frequencies of the number of gait characteristics with abnormal changes *related to GQF*.

To achieve our second objective, pwMS were stratified into two groups: 1) presenting abnormal changes in the variable analyzed (e.g., someone presenting abnormal changes in toe-off will not necessarily be someone presenting abnormal changes in step duration) and 2) not presenting abnormal changes. Afterward, these two groups (presenting and non-presenting abnormal changes) were also compared to HCs during the 6MWT through two separate two-way ANOVAs (group vs. minutes or group vs. magnitude of change, using the fatigability index, with repeated measures for minute and the magnitude). Bonferroni corrections were systematically applied when appropriate.

Results

The male-to-female ratio was higher in pwMS than in HC. PwMS were taller, with lower cognitive performance (SDMT), lower walking capacity (T25FW and 6MWT), and higher perceived fatigue (higher scores of MFIS) compared to HCs (Table 1). When comparing the pwMS walking fatigability manifestations, DWF/GQF was more disabled than NWF ($p=0.019$). Also, the DWF/GQF walked less in the 6MWT ($p<0.001$) and perceived their walking was worse ($p=0.003$) when compared to the GQF and NWF groups (Table 1).

Table 1. Mean±SD (for parametric) and median [range] (for non-normal distributed variables) for anthropometric and clinical features of people with multiple sclerosis (pwMS) and healthy controls (HC).

	pwMS (n=88)	HC (n=47)	P- value (pwMS vs. HC)	DWF (n=2)	DWF/GQF (n=35)	GQF (n=27)	NWF (n=24)	P- value (DWF vs. DWF/GQF vs. GQF vs. NWF)
EDSS (0-10)	4 [0-6.5]	-	-	4.75[4-5.5]	4.5[2-6.5] #	4[1-6.5]	3[0-6.5]	**0.030**
MS type (RR/SP/PP/NP)	63 /17/5/3	-	-	2/0/0/0	22/8/2/3	17/8/2/0	21/1/1/0	0.604
Assistive Device (Yes/No)	21/67	-	-	0/2	11/24	7/20	3/21	0.321
MSWS-12 (%)	64[22-100]	-	-	62[48-76]	81[29-100] #†	66[22-86]	56[22-96]	**0.005**
Sex (Female/Male)	59/29	39/8	**0.046**	2/0	23/12	16/11	17/7	0.168
Age (years)	49 [21-70]	46 [25-60]	0.058	53±5	49.3±9.3	48.2±12.1	46.5±14.1	0.762
Height (m)	1.68 ± 9.28	1.65 ± 8.4	**0.035**	1.69±0.01	1.69±0.09	1.69±0.09	1.68±0.10	0.992
BMI (kg/m^2)	25 [15-67]	24 [18-73]	0.300	27[25-30]	25[15-67]	25[19-34]	23[18-41]	0.286
Weight (kg)	72 [43-159]	65 [45-165]	0.089	79[70-88]	75[43-159]	77[44-103]	66[49-123]	0.217
SDMT (N)	49.1 ± 13.5	59.9 ± 9.9	**<0.001**	42[28-56]	49[19-65]	46[16-65]	54[28-83]	0.093
T25FW (s)	5.9 [3.2-16.7]	3.9 [2.6-5.9]	**<0.001**	6.6[4.0-9.1]	6.4[3.3-16.6]	6.0[3.2-16.7]	4.7[3.7-8.5]	0.088
6MWT (m)	375.9 ± 125.3	591.3 ± 65.1	**<0.001**	422.0±103.2	312.7±111.8#	382.9±118.8	456.5±106.7	**<0.001**
MFIS-Total (0-84)	40 [0-73]	10 [0-54]	**<0.001**	30[6-54]	45[9-73]	33[2-60]	33[4-63]	0.094
MFIS- Physical (0-36)	20 [0-35]	2 [0-27]	**<0.001**	17[5-29]	23[5-35] #†	20[0-30]	18[2-30]	**0.022**
MFIS- Cognitive (0-40)	14 [0-40]	5 [0-22]	**<0.001**	10[0-20]	16[0-40]	12[0-26]	11[0-33]	0.338
MFIS-Psychosocial (0-8)	4 [0-8]	0 [0-6]	**<0.001**	3[1-5]	5[0-8]	3[0-7]	4[0-6]	0.115

Note. In **bold**, significant differences between groups, # indicates significant differences from the non-walking fatigability (NWF) group, and † indicates significant differences from the gait quality fatigability (GQF) group. Abbreviations: people with Multiple sclerosis (pwMS); Healthy controls (HC); Multiple sclerosis (MS); Symbol digit modality test (SDMT); Timed 25-foot walking (T25FW); Modified Fatigue Scale (MFIS); Multiple sclerosis walking scale (MSWS-12); relapsing-remitting (RR); secondary progressive (SP); primary progressive (PP); non-provided (NP)

Manifestation of walking fatigability

Figure 1 presents the total number of cases where the DWF or GQF happened in isolation or co-occurred in pwMS. In general, 72.8% of pwMS presented either DWF, GQF, or a combination. Specifically, isolated DWF was only observed in two pwMS, while isolated GQF was presented in 27 pwMS (Figure 1A-B). The combination of DWF and GQF was presented in 35 pwMS, and 24 pwMS did not show walking fatigability (Figure 1A-B). Figure-1A presents the frequency of cases showing abnormal changes in specific gait characteristics or in the DWI, sorted by the total distance walked in the 6MWT. The high heterogeneity in abnormal changes among pwMS highlights the different gait profiles in GQF. Higher heterogeneity is also evident in Figure-1C, which shows a wide variation in the number of affected gait characteristics, ranging from one (n=16) to nine (n=2). The supplementary material (Figure S1) presents the frequency of abnormal changes in each gait characteristic for DWF/GQF and GQF. The DWF/GQF group generally presented a higher frequency of abnormal changes for all gait characteristics, except for step duration asymmetry, compared to the GQF group.

*****Insert Figure 1 near here*****

Gait characteristics through the 6MWT

The complete statistics are presented in Table S1 (Supplementary material). Figure 2 presents the results from the gait characteristics through the 6MWT. To avoid redundancy of gait domains and given the highest prevalence of abnormal changes among pwMS, cadence, step duration, toe-off, step duration variability, and leg circumduction were selected for group comparison through the 6MWT for pwMS presenting abnormal changes vs. not presenting abnormal changes vs. HC.

The gait characteristics of healthy subjects were systematically better than the pwMS over the 6MWT. The group*minutes and group*magnitude interaction effects were significant for all variables. Post-hoc comparisons for each gait characteristic, minute-by-minute, and their magnitude are presented below.

Cadence

PwMS presenting with abnormal changes for cadence (n=39) presented a steady decline from minute 2 onwards, with systematically greater magnitude, compared to the first two minutes of the 6MWT ($p<0.001$). In HCs and pwMS without abnormal change, cadence decreased till minutes 2 and 3 but stabilized in the remainder of the test. HCs presented a higher cadence every minute compared to both groups of pwMS.

Step duration

Only pwMS with abnormal changes (n=40) presented a significant constant increase, minute-by-minute, through the 6MWT ($p<0.001$). On the other hand, both pwMS without abnormal changes (n=48) and HC increased step duration from minute 1 to minute 2 and maintained stable till minute 6. PwMS with abnormal changes presented higher step duration compared to pwMS without abnormal changes for every minute ($p<0.001$). Lower step duration was observed for HCs compared to both pwMS groups.

Step duration variability

Only pwMS with abnormal changes (n=18) in step duration variability presented significant increases from minute 1 to minutes 3 to 6 ($p<0.001$), from minute 2 to minutes 4-6 ($p<0.021$), and from minutes 3-5 to minute 6 ($p<0.033$). PwMS with abnormal changes presented similar step duration variability compared to pwMS without abnormal changes (n=70) in minutes 1 and 2 ($p>0.05$) but different from minute 3 onwards ($p<0.001$). HCs presented lower step duration variability compared to both pwMS in every minute.

Toe-off

While pwMS with abnormal changes (n=25) presented a constantly significant decrease in toe-off angle minute-by-minute ($p<0.001$), pwMS without abnormal changes (n=63) increased toe-off angle from minute 1 vs. minute 6 ($p=0.005$). A higher toe-off angle was observed in HCs compared to pwMS. PwMS with abnormal changes presented lower toe-off compared to pwMS without abnormal changes from minute 3 onwards ($p<0.001$).

Leg circumduction

PwMS with abnormal changes (n=13) in leg circumduction presented increased leg circumduction in every minute, except minute 2, compared to minute 1 ($p<0.005$), minute 2 compared to minutes 5 and 6 ($p<0.003$), minute 3 compared to minute 6 ($p=0.008$) and minute 4 compared to minute 6 ($p=0.03$). On the other hand, pwMS without abnormal changes (n=75) and HCs presented consistent leg circumduction throughout the 6MWT. PwMS with abnormal changes presented lower leg circumduction compared to pwMS without abnormal changes in minutes 1 and 2 ($p<0.031$). For the remaining (from minute 3 onwards) of the 6MWT, leg circumduction was similar among groups ($p>0.05$).

*****Insert Figure 2 near here*****

Discussion

Our study investigated the different manifestations of walking fatigability and its prevalence in pwMS considering the activity (i.e., distance walking fatigability) and body function level (i.e., gait quality fatigability) in pwMS. Walking fatigability was present in a majority of pwMS. Confirming our first hypothesis, we established that walking fatigability mainly affects the distance walked and gait quality. Changes in the temporal domain were most prevalent, with abnormal reduction in gait speed likely due to reduced cadence and increased step duration. However, increased step duration variability was also often present, suggesting reduced cortical control over time (25-27). Regarding angular metrics, changes in toe-off were common, likely relating to emerging (minimal) drop foot, followed by changes in leg circumduction. Our findings also indicated that, for GQF, the worsening of specific gait characteristics occurred gradually throughout the 6MWT, corroborating our second hypothesis.

Prevalence and manifestation of walking fatigability at the activity and body function level

As shown by our study, walking fatigability is a motor impairment that manifests in both activity and body function levels. Previous studies usually investigated either DWF(1-5, 18, 28-33) or gait characteristics(7-13) isolated, with a few exceptions(6, 14). A recent systematic review showed that the pwMS worsened in some gait characteristics at the end of the 6MWT (9). Nevertheless, these studies did not use cut-off scores to define when a worsening in gait is considered normal or abnormal

change. According to our knowledge, our study is the first to use cut-off scores provided elsewhere(15) to define GQF. However, previous studies reported that DWF is related to changes in balance(6) and that pwMS with and without DWF perceived their gait pattern disturbed at the end of the 6MWT compared to the beginning(29). Our results align with these previous studies and indicate that walking fatigability manifests in reduced distance walking and gait quality. In Figure 3, we summarize the different manifestations of walking fatigability in MS. PwMS might present DWF and GQF isolated or in combination. Still, at the same time, some pwMS will not present any abnormal changes through the 6MWT.

Walking fatigability is a complex and multifactorial motor impairment in pwMS. Previous studies suggested that walking fatigability in pwMS might be due to pacing strategy (34), knee flexor/extensors, and ankle dorsiflexor muscle strength (28, 30), exacerbation of MS-related symptoms (e.g., spasticity) (29), disability severity (1, 3), reduced central drive(35), lower neural reserve(1, 6), reduced gait automaticity(25, 26) and gait compensation(36). In our study, pwMS presenting with DWF/GQF presented higher levels of disability, less walking capacity, more perceived walking impairments, and higher frequencies of abnormal changes compared to GQF and NWF. Given the heterogeneity of abnormal changes in distance walked and gait characteristics/domains among pwMS, it is difficult to propose the underlying causes of DWF and GQF in the current study. We might consider that the mechanisms/causes of the different walking fatigability manifestations might overlap. However, analyzing the gait characteristics throughout the 6MWT might provide further information (see next section). Lastly, the higher heterogeneity among pwMS in the gait characteristics/domains changes led us to infer that walking fatigability has different gait profiles.

Gait profile is described in the ICF as a "functions of movement patterns associated with walking, running or other whole-body movements" that can include "walking patterns; impairments such as spastic gait, hemiplegic gait, paraplegic gait, asymmetric gait, limping and stiff gait pattern." Specifically, for pwMS, distinct gait profiles are observed in previous studies: spastic-paretic, uncoordinated, and unbalanced patterns(37, 38). For each gait profile, a central feature is observed; for example, spastic-paretic patterns are recognized to present a reduced range of motion(37, 38). Notably, the gait profiles in MS were defined in short walking protocols, and whether it can be translated to prolonged walking assessment and walking fatigability remained unknown. Our study provides the first evidence, based on the gait characteristics affected, that different gait profiles might be observed for walking fatigability during prolonged walking. Unfortunately, we did not measure important gait characteristics such as range of motion. Therefore, future studies should also incorporate kinematic gait characteristics.

*****Insert Figure 3 near here*****

Gait characteristics throughout the 6MWT

PwMS with GQF showed steady worsening throughout the 6MWT and after the second minute for one or more specific variables(15). Recently, we demonstrated that this pattern also occurs for DWF(3). We advise that gait characteristics and distance walked (minute by minute and applying the fatigability index) be considered when performing the 6MWT in pwMS. Knowledge of which specific gait characteristics worsen may assist in reflections on the mechanisms of walking fatigability and the optimal rehabilitation strategy. A decrease in cadence and an increase in step duration (rhythm gait domain) might indicate a loss in gait automaticity already present in pwMS(25). On the other hand,

pwMS presenting with an abnormal decrease of the toe-off angle (or flat foot) towards the end of the 6MWT might indicate an inability of the person to have proper muscle force or an increase in muscle spasticity(29) for push-off of walking, having implications for distance walked or increasing the chances of tripping. In the case of pwMS increasing step duration variability (variability domain) abnormally, it might indicate a higher use of cortical brain resources to finish the 6MWT (25-27). Changes in leg circumduction observed in our study over the 6MWT could be attributed to gait compensations to overcome fatigability effects on gait(36). In general, the abnormal changes in the domains mentioned above increase the chance of falling towards the end of the 6MWT. Rehabilitation strategies such as gait training to recover gait automaticity and increase neural capacity(39) (rhythm and variability gait domain), muscle strength training, or stretching (kinematics domain)(40) might be helpful to reduce these abnormal changes. Nevertheless, these are assumptions and should be further explored in future studies. Also, future studies may want to incorporate measures of strength and spasticity to determine if they contribute to the changes in gait over the 6MWT and part of the changes in the gait characteristics.

There may also be relevance in measuring gait characteristics over prolonged walking protocols to enhance predictor models. Previously, Goldman et al., (18) identified two groups of pwMS (low and high-risk progressors) by investigating the distance walked minute-by-minute during the 6MWT. PwMS presenting a constant decline in distance walked showed a higher risk of progression than those with a more stable distance walked throughout the 6MWT. We hypothesize that identifying those pwMS with abnormal changes in specific gait characteristics would improve the predictor model for disease progression. This methodology can help detect early mobility problems as well as progression independent of relapse activity (PIRA). However, longitudinal studies are necessary for such purposes.

Strengths and Limitations

A particular strength of this study is to be the first to use defined cut-off scores (15) to define when a change in gait characteristics during the 6MWT is (ab)normal. Although previous studies have shown worsening in gait quality during the 6MWT in pwMS (9), it is difficult to conclude if those changes exceeded abnormal thresholds. Particularly, we add to the previous knowledge, using these cut-off scores, that walking fatigability manifests in the ICF's activity and body function levels. In addition, we evaluate different gait characteristics within different gait domains. This allows for a more complete description of walking fatigability manifestation in pwMS. On the other hand, some methodological considerations have to be considered.

We did not stratify our participants according to their level of disability, MS phenotype, or walking capacity, given the limited sample size and heterogeneity of manifestation of gait quality fatigability. It is, however, known that changes in gait speed and characteristics during or immediately after the 6MWT are more prevalent and prominent in pwMS with higher disability(3, 9). Furthermore, it is acknowledged that the gait characteristics are calculated during straight-line walking without turning during the 6MWT. In a minority of cases, abnormal reductions in gait speed measured by sensors were not accompanied by abnormal reduction in distance walked at the end of the 6MWT compared to the start, which was likely related to not incorporating the turns. In other words, some patients may particularly decline in the capacity to turn 180 degrees over time, which might be more challenging for more disabled pwMS (41). Also, given logistical differences in different centers, the 6MWT in the present study was performed in corridors of different lengths (20, 25, or 30 meters), which could impact the number of turns performed and possibly the prevalence of pwMS presenting DWF (42). However, GQF was only calculated on straight-line walking and should not have been impacted by the length of the track and number of turns (42). We applied the most common 6MWT

guidelines in pwMS (24) with instructions to walk as far but safely as possible, straight-line walking and turns after 20-30 meters, as well as notifications of each minute passing. Different instructions on the walking track used (i.e., continuous vs. straight line with turning at both ends) could impact the DWF and GQF manifestation (9). Lastly, we did not evaluate psychological factors such as mood or depression as well as sleep. These factors are important and might impact the pacing strategy during the 6MWT, with people not challenging themselves to walk as fast as possible at the start of the 6MWT.

Conclusion

Walking fatigability is present in a majority of pwMS, affecting over 2/3 of pwMS, and manifests in both distance walked and gait quality changes during the 6MWT. The manifestation in gait quality is heterogeneous and varies among pwMS with different (number of) gait characteristics affected. Furthermore, the worsening of gait is steady throughout the 6MWT in those with abnormal changes. Results call for integrating gait quality measures in assessing pwMS and developing tailored rehabilitation programs.

Acknowledgment

The authors would like to thank all the study participants and clinical MS centers for participation and the physiotherapy master students of the University of Hasselt for assisting with data collection.

Funding

This study was supported by Research Foundation - Flanders (#11O5823N), Bijzonder onderzoeksfonds (#BOF22INCENT16 and #BOF20BL13), the MS LIGA Flanders (steunfonds) and the King Beaudouin foundation (fund Claire Fauconnier).

Declaration of Conflicting Interests

The Author(s) declare(s) that there is no conflict of interest.

Data availability

The data used and which support the findings of the present study are available through the corresponding author upon request.

Ethics statement

The study was approved by the Medical Ethical Committee of the University of Hasselt and the Ethical Committee of the Dokuz Eylul University (Izmir, Turkey). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

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Figure legend

Figure 1. Heat and bar plots of the frequencies of the presence of abnormal changes for each case (A), the occurrence of distance walking fatigability (DWF), Gait quality fatigability (GQF), the combination of DWF/GQF and non walking fatigability (B), number of cases per total (sum) of gait characteristic affected (C).

Figure 2. Average and standard error of specific gait characteristics through the 6-minute walking test for people with multiple sclerosis not presenting abnormal changes (solid line) and presenting abnormal changes (dotted line) for each gait characteristics. ^{1} represents significant differences from minute 1; ^{2} represents significant differences from minute 2; ^{3} represents significant differences from minute 3; ^{4} represents significant differences from minute 4; ^{5} represents significant differences from minute 5; $^{2\text{-}1}$ represent significant differences from 2-1; $^{3\text{-}1}$ represent significant differences from 3-1; $^{4\text{-}1}$ represent significant differences from 4-1; $^{5\text{-}1}$ represent significant differences from 5-1; $^{6\text{-}1}$ represent significant differences from 6-1.

Figure 3. Walking fatigability manifestations where, in the present study, we observed only distance walking fatigability (1), only gait quality fatigability (2), the combination of both distance and gait quality fatigability (3) and non-walking fatigability (4).