Exercise-induced changes in gait kinematics in multiple sclerosis with minimal neurological disability

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Abstract

Background

Exercise-induced gait deterioration is a frequently encountered symptom that limits ambulation throughout the clinical course, becoming more prominent with increasing neurological disability in people with MS (pwMS).

Objective

We attempted to objectively document exercise-induced gait changes in pwMS with minimal neurological disability and stable disease.

Methods

Gait kinematics and spatio-temporal parameters were recorded using 3D motion analysis before and after a 20-minute treadmill walk (Group A, n=15)/run (Group B, n=15) at a self-selected speed in pwMS and compared with healthy controls (n=15).

Results

Gait analysis revealed a significant decrease in peak ankle dorsiflexion in swing of the most affected leg, post-exercise task, in both Group A (EDSS 2.5-3.5) and Group B (EDSS 1-2.5) and not in healthy controls. Fourteen out of 30 MS participants showed an exercise-induced gait deterioration, based on minimal detectable change. Pre-exercise gait parameters in Group A showed a significantly higher peak dorsiflexion in swing with shorter step length and higher cadence, whereas Group B was comparable to healthy controls.

Conclusion

The detection of exercise-induced gait deterioration (foot drop) in pwMS with minimal neurological disability and stable disease indicates the potential of gait kinematics, before and after an exercise task, to monitor subtle neurological deficits from an early stage of MS.

Key words:

Multiple sclerosis, minimal disability, gait kinematics, exercise, foot drop, fatigability

1. Introduction

Gait impairments are a common feature of MS with approximately 85% of people with MS (pwMS) reporting that they experience walking difficulties (Kelleher et al., 2010, Bethoux and Bennett, 2011). Exercise-induced gait deterioration, which could be a sign of walking related performance fatigability, frequently limits ambulation, particularly in those with moderate neurological disability (Burschka et al., 2012, Leone et al., 2016, Shema-Shiratzky et al., 2019, Engelhard et al., 2016). Several studies have demonstrated the occurrence of exercise-induced fatigability in pwMS using a variety of outcome measures (Severijns et al., 2017). Three-dimensional (3D) gait analysis has been used to capture exercise-induced gait deterioration, especially in the ankle joint in pwMS with Expanded Disability Status Scale (EDSS) > 3 (Sehle et al., 2014, McLoughlin et al., 2016, van der Linden et al., 2018). However, to the authors' knowledge there is no evidence as to whether exercise-induced deterioration in joint kinematics during gait also occurs in pwMS with minimal neurological disability.

Anecdotal reports in clinical practice indicate that a subset of pwMS, with no impairment affecting daily walking performance and who are regularly engaged in exercise (e.g. walking/running), experience a transient phenomenon during exercise that often manifests as foot drop (decreased dorsiflexion during the swing phase of gait) (Sheridan and Bowditch, 2019). The involvement of distal lower limbs in pwMS has been proposed to reflect a length dependent pathophysiological process, which preferentially impacts the CNS reverse of the long corticospinal tracts to the lower limbs compared with upper limbs and bulbar musculature (Giovannoni et al., 2017). Although this reversible phenomenon resolves after cessation of exercise or a short period afterwards, it often becomes more prominent over time and increasingly limits ambulation. An objective measurement and improved understanding of the exercise-induced gait deterioration in this group of patients may allow the detection of early disease progression in the absence of a decrease in walking performance measured by more traditional outcomes such as the Timed 25 Foot Walk (T25FW).

Therefore, the aim of this study was to investigate exercise-induced changes of gait kinematics in pwMS with minimal neurological disability (EDSS up to 3.5). This study examined changes in gait kinematics and spatiotemporal parameters pre- and post- 20-minutes of treadmill walking (Group A) and running (Group B) at a self-selected speed in two groups of pwMS as well as healthy controls. The focus of this study is on the ankle kinematics during the swing phase as this is the joint were exercise induced gait deterioration has been shown to be the most prominent (McLoughlin et al., 2016, van der Linden et al., 2018, Sheridan and Bowditch, 2019). We hypothesised that pwMS with minimal neurological disability show exercise-induced gait deterioration unlike healthy controls.

2. Material and Methods

2.1 Participants

Participants with MS and minimal neurological disability (n=30) were recruited from the Anne Rowling Clinic (ARC), Edinburgh, and the healthy controls (n=15), age matched for the running task (Group B), were recruited through advertising at Queen Margaret University and University of Edinburgh. Inclusion criteria for participants with MS were: aged >18 years, MS diagnosed according to the revised MacDonald criteria (Thompson et al., 2018), EDSS 0-3.5, absence of clinical relapse(s) for 2 years and no new lesions on MRI head and cervical spine for at least 6 months preceding the study with or without disease modifying therapy (stable MS) and engaged in regular exercise [walking at least 2 miles weekly and without stopping (Group A) or at least 30 minutes of continuous running weekly (Group B)]. Healthy controls were aged >18, without a diagnosis of MS and required to regularly exercise (run for at least 30 min weekly). The exclusion criteria were comorbidities such as neurological conditions other than MS, those taking Fampridine, cardiovascular disease, respiratory disease such as asthma, metabolic disorders such as diabetes and thyroid disease, and peripheral vascular disease. Ethical approved was granted for this study by the South East Scotland Research Ethics Committee 02 (REC reference number: 15/SS/0088). All participants provided written consent prior to taking part in the study. All procedures were conducted in accordance with the declaration of Helsinki.

2.2 Procedures

Participants in the MS groups and healthy controls were invited to attend the gait analysis laboratory at Queen Margaret University. MS participants were sent two questionnaires to complete [Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009) and the Fatigue Severity Scale (FSS) (Krupp et al., 1989) prior to their first visit. The first visit was for the participants to become familiar with the laboratory setting and walking/running on a treadmill as well as to perform the Nine-Hole Peg Test (9-HPT) once and the T25FW twice with the average of the two taken for analysis. In the next visit all participants performed gait analysis pre- and post-exercise task. The exercise task comprised of walking (Group A) or running (Group B and healthy controls) on the treadmill for a maximum of 20 minutes at a self-selected speed that was perceived

as their usual walking or running speed. Participants had to wear a harness (Wingman Harness, USA) that was attached to the ceiling in order to prevent falling. All participants were given five minutes on the treadmill for warm up and to establish a speed that they were comfortable with prior to the commencement of the 20-minute exercise task. All participants were allowed to adjust the speed at any point during the task and any changes in speed and the time at which this occurred were recorded. Participants could stop the test at any point during these 20 minutes, without having to provide a reason. During the 20-minute exercise task, all participants were asked to rate their perceived exertion, affective valence and perceived fatigue levels every four minutes. For rating of the perceived exertion, the Borg Scale 15-point scale was used (Borg, 1982). Affective valence (pleasure/displeasure one feels) was rated through the Feeling Scale (Hardy and Rejeski, 1989) and perceived fatigue was rated through a Visual Analogue Scale ranging from 0 (no fatigue at all) to 10 (maximum fatigue) (Lee et al., 1991). To assess routine daily activity level between visits to the gait laboratory, including the regular walks and runs, participants with MS were given an ActivPal^{TM} activity monitor (PAL Technologies Ltd, Glasgow, UK) and were asked to wear this for at least five consecutive days.

For the recording of gait before and following completion of the exercise task, we used 3D gait kinematics with an eight camera Vicon Nexus system. In total 15 reflective markers (9mm) were attached to all participants' pelvis and lower limbs. Markers were attached to the pelvis (anterior superior iliac spines and sacrum), lateral epicondyles of the femur just above the joint line and lateral aspects of the thigh and tibia. Foot markers were attached to the point between the second and third metatarsal heads, the of the lateral malleolus and the calcaneum in vertical alignment with the toe marker according to the Helen Hays marker set (Kadaba et al., 1990). All participants performed six trials of barefoot walking over a distance of around 7m at their usual comfortable walking pace during which the 3D coordinates of the markers were recorded at a sample frequency of 100Hz.

2.3 Kinematic data processing

Gait kinematics and spatiotemporal parameters were derived using the Vicon Plug-in-Gait software (Vicon Motion Systems, Oxford, UK) and a custom-written Matlab script. The average of the parameters of the six gait cycles for the most and least affected limb in the MS groups and the left leg for the healthy control group was used for analysis. The most affected limb was identified based on post-exercise kinematics and the other limb was identified as the least affected leg of the pwMS.

2.4 Statistical analysis

The assumption of normality of the data was checked and confirmed by visual inspection of the q-q plots and box plots of the data and by the Shapiro-Wilks test. Paired t-tests were performed in order to determine whether there were differences between the pre- and post-exercise gait kinematic and spatiotemporal parameters in both groups of pwMS and the healthy control group. Further, independent t-tests were carried out to examine whether differences exist between the gait parameters before the exercise task between the Group A and healthy controls and between the Group B and healthy controls.

In order to determine whether exercise-induced fatigability was clinically significant at an individual level, we used the difference in the gait kinematics pre- and post-exercise task and the minimal detectable change (MDC). The MDC values were established in our previous study of people with MS and EDSS 0-3.5 that was a subgroup of the participants in the present study (Andreopoulou et al., 2019). The MDC value, calculated based on the standard error of measurement of an instrument, provides the cut-off points above which a change can be regarded as not due to random error (de Vet et al., 2006).

3. Results

3.1 Participants

The EDSS of our MS participants with minimal neurological disability (EDSS 0-3.5), segregated between 2.5-3.5 in Group A while Group B showed an EDSS range of 1.0-2.5 (Table 1). All but 2 MS participants had relapsing MS. The mean age of Group A was higher than the healthy controls, whereas the mean age of Group B was comparable (Table 1). The majority of Group A (11/15) and Group B (13/15) were on disease modifying therapy (DMT) and all had stable MS, defined as free from relapse for at least 2 years preceding the study and no new MRI lesions in the preceding 6 months (Table 2). Of all MS participants, 29 had no new lesions in the preceding 2 years.

Overall, both MS groups were experiencing mild fatigue on average according to the cut-off value for the total score of the FSMC, while none of the MS groups on average reached the cut-off value for the FSS indicating that our MS participants with minimal neurological disability were not experiencing severe self-reported fatigue (Table 1).

Gait kinematics of the most affected limb, as identified by post-exercise changes, were not significantly different pre-exercise in Group B compared with healthy controls (Table 3). In Group A, only peak dorsiflexion in swing of the most affected limb was higher pre-exercise compared with healthy controls.

Table 1 Demographic characteristics for pwMS and healthy control group.

	Group A (n=15)	**Group B (n=15)**	**Control group (n=15)**
Female/Male, n	14/1	9/6	8/7
Age, years	49.0 (25-72)	41.0 (28-70)	41.8 (29-65)
EDSS range	3.0 (2.5-3.5)	1.5 (1.0-2.5)	-

RR/PP, n	13/2	14/1	-
Disease duration, years, mean (SD)	15.9 (±8.8)	14.8 (±11.1)	-
T25FW, s	5.0 ±0.6	3.9 ±1.0	-
9HPT (Dominant/Non-Dominant), s	26.2 ±5.5/27.2 ±5.8	24.3 ±3.8/24.5 ±2.6	-
Daily step count, n	7706 (3719-12205)	11799 (3962-18832)	-
$FSMC_{tot}$ (20-100)	49.9 ±12.7	45.5 ±18.1	-
$FSMC_{cognitive}$ (10-50)	20.3 ±7.9	22.3 ±9.9	-
$FSMC_{physical}$ (10-50)	29.7 ±6.8	23.1 ±8.9	-
FSS (9-63)	33.8 ±12.0	28.6 ±15.7	-
Baseline DFMA (°)	10.4 ±3.1	7.7 ±2.9	7.0 ±2.2
Baseline WS (m/s)	1.21 ±0.1	1.29 ±0.2	1.24 ±0.2

Group A: MS participants that undertook a 20-minute treadmill walking task. Group B: MS participants that undertook a 20-minute treadmill running task.

Abbreviations: 9HPT: 9 Hole Peg Test; EDSS: Expanded Disability Status Scale; FSMC: Fatigue Scale for Motor and Cognitive Function; FSS: Fatigue Severity Scale; T25FW: Timed 25 Foot Walk; RR: Relapsing Remitting; PP: Primary Progressive; SP: Secondary Progressive.

Table 2 Individual characteristics of pwMS with minimal neurological disability.

Case No	Age (M/F)	MS subtype	DD (yrs)	EDSS	T25FW (s)	MRI	DMT	Exercise duration (min)	>MDC (º)
1	59F	RMS	38	3.5	4.8	N	None	20	Y (-6.03)
2	47F	RMS	19	3.5	5.8	N	None	20	Y (-2.50)
3	54F	RMS	2	3.0	4.9	N	DMF	20	Y (-3.49)
4	47F	RMS	10	3.0	4.9	N	DMF	20	Y (-2.89)
5	60M	PPMS	7	3.0	5.03	N	None	20	N (-1.35)
6	25F	RMS	7	2.5	5.2	N	DMF	20	N (0.31)
7	46F	RMS	19	2.5	5.1	N	DMF	20	Y (-6.03)
8	72F	RMS	23	3.0	6.3	N	Fingo	20	N (0.59)
9	51F	RMS	6	3.5	4.65	N	DMF	20	Y (-2.81)
10	53F	RMS	7	2.5	4.15	N	DMF	20	N (0.30)
11	40F	RMS	13	3.0	4.75	N	Fingo	20	N (-1.44)
12	51F	PPMS	9	3.0	5.2	N	none	20	Y (-3.61)
13	47F	RMS	22	2.5	5.1	N	DMF	16	N (-1.45)
14	57F	RMS	19	2.5	5.35	N	Avonex	20	Y (-4.35)
15	40F	RMS	18	2.5	3.9	N	Fingo	20	N (-0.47)
16	49M	RMS	26	1.5	4.7	N	None	20	N (-0.53)
17	70M	RMS	42	2.5	4.6	N	None	20	N (3.10)
18	48F	RMS	19	1.5	2.2	N	DMF	20	N (0.57)
19	44F	RMS	18	1.0	2.1	N	Copaxone	20	N (-0.88)
20	42F	RMS	20	2.0	3.3	N	Tysabri	20	Y (-3.50)

21	50F	RMS	25	2.0	4.2	N	Extavia	20	Y (-3.29)
22	34M	RMS	11	1.5	4.2	N	DMF	20	Y (-2.94)
23	39M	RMS	6	1.0	3.7	N	DMF	20	N (-0.80)
24	41M	RMS	2	2.5	4.7	N	DMF	20	N (-2.39)
25	41F	RMS	15	1.0	4.8	N	DMF	20	Y (-4.38)
26	30F	RMS	8	1.5	4.8	N*	Fingo	20	N (1.22)
27	39M	RMS	9	1.0	2.8	N	Aubagio	20	Y (-3.03)
28	39F	RMS	22	1.0	4.3	N	DMF	20	N (0.17)
29	28F	RMS	10	2.5	3.9	N	Fingo	9	Y (-4.68)
30	36F	RMS	2	1.5	5.3	N	copaxone	20	N (-1.79)

MS participants 1-15 consisted Group A and 16-30 consisted Group B.

*MS participant 26 showed 2 new lesions between 6-18months prior to entry into the study. All other MS participants showed no new MRI lesions (N) during the 24 months preceding the study entry. None of the MS participants had a clinical relapse during the preceding 24 months, prior to starting the study.

DMF: Dimethyl fumurate, DMT: disease modifying therapy (either the most recent agent or none in the 2 years prior to the study). PPMS: Primary Progressive MS. RMS: Relapsing MS.

3.2 Exercise task characteristics

All, except two participants with MS (one from Group A and one from Group B), completed the 20-minute self-selected exercise task on the treadmill (Table 4). As expected, the average speed during the 20-minute treadmill exercise task was slower for the Group A compared with healthy individuals ($p<0.01$), who consequently covered more distance during the exercise task. On the other hand, average speed and distance covered in 20 minutes in Group B were comparable to the healthy controls. Subjective measurements showed that on average the change in peak exertion was less in Group B and fatigue indicated by visual analogue scale was also less in Group B relative to healthy controls although did not reach statistical significance. Subjective measurements of

Group A, however, was comparable to that of healthy controls despite the difference in the exercise task.

Table 3 Gait kinematic and spatiotemporal characteristics of all groups before and after a 20-minute self-selected exercise task [Mean (SD)].

	Group A (n =15)		**Group B (n=15)**		**Control group (n=15)**	
	Pre-walk	Post-walk	Pre-run	Post-run	Pre-run[§]	Post-run[§]
Kinematic parameters						
DFMA (°)	10.4 ±3.1	8.1 ±3.8**	7.7 ±2.9	6.2 ±3.8*	7.0 ±2.2	7.1 ±2.7
DFLA (°)	11.0 ±3.4	11.0 ±3.7	8.7 ±2.7	8.6 ±2.7	-	-
ICMA (°)	4.9 ±2.5	2.2 ±3.8***	0.4 ±4.6	0.2 ±5.1	1.9 ±3.0	2.2 ±3.4
ICLA (°)	4.5 ±3.1	4.1 ±3.8	1.4 ±5.6	2.3 ±5.8	-	-
Spatiotemporal parameters						
WS (m/s)	1.21 ±0.1	1.15 ±0.2	1.29 ±0.2	1.31 ±0.2	1.24 ±0.2	1.29 ±0.2**
Cadence (steps/min)	120 ±6	116 ±10	118 ±10	119 ±9	114 ±10	116 ±10**
SLMA (m)	0.60 ±0.05	0.59 ±0.06	0.66 ±0.08	0.67 ±0.09	0.65 ±0.05	0.66 ±0.05*
SLLA (m)	0.60 ±0.05	0.59 ±0.05	0.65 ±0.07	0.65 ±0.08	-	-

*p<0.05, **p<0.01, ***p<0.001 indicate a significant difference between pre-exercise and post-exercise parameters for all groups. [§]data from the left leg was used for analysis in healthy controls.

Abbreviations: DFMA: peak dorsiflexion in swing of most affected limb; DFLA: peak dorsiflexion in wing of least affected limb; ICMA: ankle angle at initial contact of most affected limb; ICLA: ankle angle

at initial contact of least affected limb; SLMA: step length of most affected limb; SLLA: step length of least affected limb; WS: walking speed.

3.3 Pre-post exercise gait changes

The main objective was to explore the differences between gait characteristics in pwMS before and directly after a 20-minute exercise task on a treadmill at a self-selected speed. None of the knee or hip kinematics showed statistically significant changes between pre- and post-exercise in the MS groups not the healthy controls. In Group A, the peak dorsiflexion in swing of the most affected limb decreased significantly post-exercise by 2.3° [$t(14)=4.274$, $p=0.001$, 95% CI (1.17-3.52)] and ankle angle at initial contact of the most affected limb significantly decreased by 2.7° [$t(14)=4.809$, $p<0.0001$, 95% CI (1.48-3.87)]. The Group B had a significant decrease of 1.5° [$t(14)=2.703$, $p=0.017$, 95% CI (0.32-2.76)] for peak dorsiflexion in swing post-exercise but not the ankle angle at initial contact (Table 4). Kinematic parameters of the least affected leg pre-post exercise did not change significantly in both MS groups. As can be seen from Table 3, there were no statistically significant differences between the pre- and post-exercise kinematic parameters in the healthy individuals. Spatiotemporal parameters in healthy controls detected a statistically significant increase in walking speed [$t(14)=-3.552$, $p=0.003$, 95% CI (-0.08 -0.02)], cadence [$t(14)=-3.822$, $p=0.002$, 95% CI (-4.3 -1.21)] and step length of the left limb [$t(14)=-2.368$, $p=0.033$, 95% CI (-0.02 -0.001)] post-exercise compared with pre-exercise self-selected walking speed. In contrast, we did not detect a significant difference in walking speed, cadence and step length of both MS groups post exercise compared with their pre exercise measurements (Table 4).

Table 4 Exercise task and self-reported response characteristics for the three groups.

	Group A (n=15)	**Group B (n=15)**	**Control group (n=15)**
Average speed (km/h)	4.5 ±1.02	8.2 ±2.0	9.8 ±2.6
Total distance (km)	1.56 ±0.4	2.53 ±0.7	2.88 ±0.8
Exercise duration (mins)	20*	20*	20

Peak RPE (6-20)	15	14	17
ΔRPE (6-20)	9	4.6	11
ΔFeeling Scale (+5 to -5)	-6.0	-6.0	-5.0
ΔVAS Fatigue (0-10)	-8.0	-3.0	-7.0

Abbreviations: ΔRPE: change over 20-minutes of Rating of Perceived Exertion; ΔVAS: change over 20-minutes of Visual Analogue Scale. Exercise duration indicates median. All except one from Group A and one from Group B completed the 20-minute exercise task. One MS participant [13] exercised for 16 minutes and one MS participant [29] exercised for 9 minutes (Table 2).

At an individual level, eight of the 15 in Group A and six of the 15 in Group B showed a deterioration in peak dorsiflexion in swing of the most affected limb that exceeded the MDC value after the completion of the 20-minute treadmill exercise task at a self-selected speed. None of the healthy controls demonstrated a decrease in dorsiflexion in swing after the exercise task that exceeded the MDC (Figure 1).

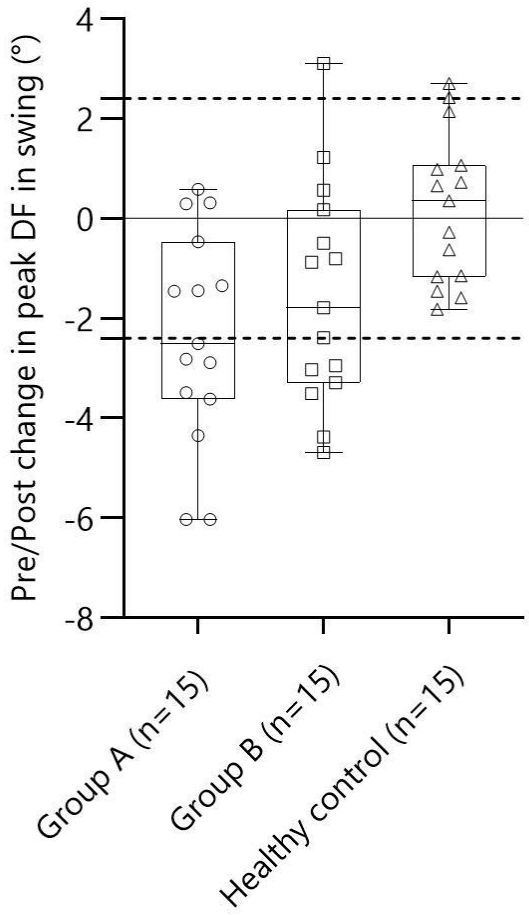

Figure 1 Difference in peak dorsiflexion in swing pre and post exercise at an individual level. The dotted lines represent the MDC (2.4°). Box plots indicate 25th to 75th percentiles with median and minimum to maximum values.

4. Discussion

This is the first study to report exercise-induced gait deterioration, using 3D kinematics, in pwMS with EDSS up to 2.5. A significant decrease in peak ankle dorsiflexion in swing following a 20-minute exercise task at a self-selected speed was demonstrable in the most affected limb in Group B (EDSS 1-2.5) as well as Group A (EDSS 2.5-3.5). Previously, only two studies investigated exercise-induced gait deterioration in pwMS with minimal neurodisabiltiy utilizing instrumented gait analysis with the 6-minute walk test (6MWT) (Engelhard et al., 2016) and a treadmill walking test until exhaustion or up to 60 minutes (Sehle et al., 2014). However, neither of the studies measured ankle dorsiflexion. Decreased ankle dorsiflexion in swing results in a reduced clearance that can lead to trip and falls and is therefore an important measure of walking performance in activities of daily living. Studies including pwMS with moderate neurological disability (EDSS 3-6 and 4-6) reported a significant decrease in peak ankle dorsiflexion in swing and at initial contact of the most affect limb following a 6MWT (McLoughlin et al., 2016, van der Linden et al.,2018). Thus, our observation of exercise-induced foot drop induced by 20-minute treadmill exercise in both MS groups with minimal neurological disability, together with the previous studies of fatigability in moderately disabled pwMS (McLoughlin et al., 2016, van der Linden et al.,2018), indicates that exercise-induced deterioration of ankle dorsiflexion is detectable across the clinical course of MS when an appropriate perturbation, i.e. sufficiently demanding, is applied.

So far, the majority of studies that have investigated exercise-induced gait deterioration in pwMS have used walking indices, such as slowing down of walking speed over a 6MWT or 12-min walk test (12MWT) (deceleration index) and distance covered during first and last minute of 6MWT and 12MWT (distance walking index), instead of kinematics (Burschka et al., 2012, Phan-Ba et al., 2012, Leone et al., 2016, Shema-Shiratzky et al., 2019). These studies involving pwMS with minimal disability show mixed results with some studies demonstrating exercise-induced decrease in walking speed during the 6MWT (Leone et al., 2016) and 12MWT (Burschka et al., 2012), while others did not find a decrease in walking speed with the 6MWT (Burschka et al., 2012, Shema-Shiratzky et al., 2019) or 500m walk (Phan-Ba et al., 2012). These conflicting results may be explained by the variability in exercise protocol used, indicating the need for a more demanding protocol for those with minimal disability. In our study, which measured gait kinematics, we opted

for a 20-minute exercise protocol and adapted it to the participant's (walking or running at a self-selected) speed that was thought to be both sufficiently demanding and feasible from safety and ethical point of view. A limitation of using walking indices based on walking speed for measuring exercise-induced gait deterioration is that they do not capture the subtle changes in gait pattern induced by exercise. Anecdotal reports from pwMS with exercise-induced deterioration suggest that gait changes occur over the duration of the exercise task and these include the development of a reversible foot drop and difficulty controlling the lower limb(s) as well as lower limb weakness (Sheridan and Bowditch, 2019), indicating the need for techniques such as gait analysis and electromyography.

Pathophysiology of exercise-induced fatigability in MS is likely to be multifactorial, involving both the CNS and skeletal muscle (Kos et al., 2008). Demyelination, axon degeneration and inflammation have been implicated in the pathogenesis of fatigue in MS. Studies from a number of independent groups, indicating mitochondrial perturbations within neurons in MS, implicate a state of neuronal energy failure in the CNS (Mahad et al., 2015). Both the multifocal lesions, metabolic changes that result from demyelination and the axonopathy affect the long corticospinal tracts to the lower limbs to a greater extent than upper limbs and bulbar musculature. This explains the length dependent loss of CNS reserve manifesting as exercise-induced foot drop in pwMS with minimal disability (Giovannoni et al., 2017). In both of our MS groups, exercise-induced rise in core body temperature may impair nerve conduction and trigger the reversible foot drop due to Uhthoff's phenomenon (Frohman et al., 2013). A case study that investigated intermittent foot drop, which was induced by running, in a MS patient with minimal neurological disability failed to identify alternative causes such as muscle and peripheral nerve abnormalities in nerve conduction studies and lumbar canal stenosis on MRI (Sheridan and Bowditch, 2019). In pwMS with moderate to severe disability, secondary changes in skeletal muscle due to restricted mobility may contribute to the exercise-induced fatigability (Abadi et al., 2009). However, this is less likely to be present in those with mild neurological disability. Future studies are needed to understand the CNS driven mechanism(s) of exercise-induced fatigability in pwMS with minimal neurological disability.

In our MS participants, exercise-induced gait deterioration occurred independently of relapse, as all participants had stable MS based on the absence of relapses in the preceding 2 years as well as lack of MRI activity in the preceding 6 months. However, they did not have a benign form of MS, as 24 out of 30 participants were on DMT for active relapsing MS. Furthermore, although the participants in our study exercised regularly (weekly) average daily step count of our participants (i.e. 7706-11799 steps) is comparable to those with minimal neurological disability in a recent longitudinal study (i.e. ≈8000 steps) (Block et al., 2019). Therefore, the findings of this study are likely to be applicable to the wider MS population with minimal neurological disability and optimally treated disease.

Our results show that 14 participants developed an exercise-induced decrease in peak dorsiflexion in swing that exceeded the MDC, while 16 did not. There are multiple possible reasons for some of our MS participants with minimal neurological disability not showing exercise-induced foot drop. The exercise task, walking/running on a treadmill at a self-selected speed, was limited to 20 minutes and some of the participants may have shown exercise-induced gait deterioration following a more prolonged perturbation and/or a faster walking/running speed. Further, post-exercise gait in some of the participants, particularly in Group B, may have recovered during the three-minute time interval required to change from the shod treadmill walking/running to the barefoot gait analysis trials. It is recommended that future studies analyse participants' gait kinematics throughout the exercise task as well as pre and post exercise.

5. Conclusion

In summary, this study shows that exercise-induced gait changes can be objectively measured using the analysis of gait kinematics in pwMS with minimal neurological disability and stable disease, including for the first time in those with EDSS 1-2.5. Therefore, gait kinematics in relation to an exercise task may offer the potential to monitor subtle clinical changes in pwMS and offer personalised therapeutic interventions from an early stage of MS.

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