Gait & Posture 44 (2016) 178–183

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

The correlation between symptomatic fatigue to definite measures of gait in people with multiple sclerosis

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ARTICLE INFO

Article history:
Received 20 October 2014
Received in revised form 21 May 2015
Accepted 10 December 2015

Keywords:
Multiple sclerosis
Fatigue
Gait
Spatiotemporal
Walking

ABSTRACT

There is a general consensus relating to the multidimensional aspects of fatigue in people with multiple sclerosis (PwMS), however, the exact impact of this symptom on gait is not fully understood. Our primary aim was to examine the relationship between definite parameters of gait with self-reported symptomatic fatigue in PwMS according to their level of neurological impairment. Spatio-temporal parameters of gait were studied using an electronic walkway. The Multiple Sclerosis Walking Scale (MSWS-12) questionnaire, a patient-rated measure of walking ability was collected. The Modified Fatigue Impact Scale (MFIS) questionnaire was used to determine the level of symptomatic fatigue. One hundred and one PwMS (61 women) were included in the study analysis. Subjects were divided into mild and moderate neurological impaired groups. Fatigue was correlated with 5 (out of 14) spatiotemporal parameters. However, correlation scores were all <0.35, thus considered as weak correlations. In the mild group, the double support period was the only variable positively correlated to fatigue (Spearman's rho = 0.28, $P = 0.05$). In the moderate group, step and stride length were solely negatively correlated to fatigue (Spearman's rho = 0.32, $P = 0.03$). In contrast to the definite gait parameters, the MSWS-12 self-questionnaire was moderately positively correlated to the level of fatigue. Scores for the total, mild and moderate groups were 0.54, 0.57 and 0.51; $P < 0.01$, respectively. The present results indicate that modifications in spatio-temporal parameters of gait are not closely related to symptomatic fatigue in PwMS. On the contrary, the self-reported MSWS-12 questionnaire is predisposed to level of fatigue in PwMS.

1. Introduction

Fatigue is one of the most common and debilitating impairments associated with multiple sclerosis (MS), an idiopathic inflammatory demyelinating disease of the central nervous system, primarily affecting young women. Fatigue has been reported by 53–92% of people with MS (PwMS) and is often described as more severe than pain or physical disability, limiting routine daily activities and reducing quality of life. [1]

Several pathophysiological mechanisms for fatigue such as dysregulation of the immune system, impaired nerve conduction and neuro-endocrine and neurotransmitter changes [2–4] have been suggested as sources of fatigue in PwMS, however, the exact mechanism and impact on other MS symptoms is still unknown.

There is a general consensus regarding the multidimensional aspects of fatigue in PwMS, however, the exact impact of this symptom on gait is not fully understood. Most PwMS (85%) complain of gait disturbances [5] and more than two-thirds do not retain the ability to walk 20 years after diagnosis [6]. Clarifying the relationship between fatigue and walking can assist both the patient and the clinical management team in terms of assessing disease progression and developing rehabilitation strategies directed at reducing the negative impact of these two disabling sequels of MS.

Previous studies have examined the association between fatigue and gait [7–12] in the MS population. Sacco et al. [7] revealed a significant negative correlation between velocity ($r = -0.54$), cadence ($r = -0.44$) and stride length ($r = -0.5$) with reported fatigue in 24 PwMS. Similar findings were observed by Motl et al. [8] and Sandroff et al. [9] in a relatively large group of PwMS. In contrast, Morris et al. [10] reported that self-rated fatigue significantly increased from morning to afternoon, whereas the footstep patterns remained the same. These findings are in

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http://dx.doi.org/10.1016/j.gaitpost.2015.12.014
0966-6362/

agreement with Krupp et al. [11] who reported no direct relationship between neurological disability and perceived fatigue. Schwartz [12] also found no direct relationship between self-reported fatigue and ambulation. Furthermore, Alvarenga-Filho et al. [13] concluded that perception of fatigue occurs in PwMS independently of neurological impairment. Thus, it seems that the evidence regarding the association between gait and fatigue in PwMS is still controversial.

It is worth noting that these studies comprised several limitations, i.e. a small sampling group and employing a single general measure of gait, limiting an in-depth view of walking capabilities in PwMS. Moreover, the majority of these studies included PwMS with a wide range of ambulation disabilities, (i.e. those without clinical impairment and PwMS who could ambulate only 20 m with walking aids). This relatively wide walking diversity reduces the ability to draw accurate information as to various neurological symptoms in PwMS in addition to properly generating goal-directed intervention programs. Recently, Feys et al. demonstrated that spatio-temporal gait parameters vary according to speed instructions and walking history in PwMS with different ambulatory dysfunctions, suggesting that future trials should be executed on homogeneous subgroups of the MS population [14].

Therefore, the primary aim of this investigation was to examine the relationship between definite parameters of gait with self-reported symptomatic fatigue in PwMS according to the level of neurological impairment. We hypothesized that since both fatigue and neural control of gait are mediated by supraspinal and spinal inputs [4], a significant relationship between reported fatigue levels and alterations in the gait pattern of PwMS would be found.

2. Methods

2.1. Study design and participants

We evaluated retrospective data from the medical charts of PwMS documented at the Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, Israel. Inclusion criteria required (1) a neurologist-confirmed diagnosis of definite relapsing-remitting MS according to the revised McDonald criteria [15], (2) <7 on the Expanded Disability Status Scale (EDSS), equivalent to ambulating for about 20 m without resting, (3) relapse-free for at least 30 days prior to testing, (4) PwMS who had filled out the Multiple Sclerosis Walking Scale (MSWS-12) and Modified Fatigue Impact Scale (MFIS) questionnaires, (5) and had performed a gait lab examination using the GAITRite electronic mat.

Exclusion criteria included (1) orthopedic disorders that could negatively affect mobility, (2) no history of psychiatric problems, (3) pregnancy, (4) blurred vision, (5) cardiovascular disorders, (6) respiratory disorders, (7) or taking steroids or fampridine.

One hundred and one relapsing-remitting patients diagnosed with MS (61 women and 40 men, average age 41.8, SD = 14.8) met these criteria and were included in the study analysis. The study was approved by the Sheba Institutional Review Board. All participating subjects signed an informed consent form for use of their data in the research projects.

2.2. Gait analysis

Spatio-temporal parameters of gait were studied using the GAITRite^{TM} system version 4.0.3 (CIR Systems, Inc. NJ, USA), which consisted of a 4.6 m long electronic walkway containing 2304 compression-sensitive sensors arranged in a grid pattern. As the subject ambulated across the walkway, pressure was exerted by his feet, thus activating the sensors. Simultaneously, targeted software utilized special algorithms to automatically group the activated sensors and form footprints. The system integrated all footprints and provided the following spatio-temporal parameters: gait velocity, cadence, step/stride length, step/stride time, heel to heel base of support, swing/stance time, single/double time and percentage according to gait cycle. A single valid walking trial was defined once the participant independently walked across the electronic mat in one direction without stopping. Each participant performed six consecutive walking trials. Gait parameter scores were individually calculated for each pass. The values from all trials were then averaged to produce the final results.

The MSWS-12 is a patient-rated measure of walking ability. Questions were based on the PwMS's walking limitations during the past 2 weeks. Each item was scored on a 1 to 5 scale - the higher the score, more difficulties. The MSWS-12 has been shown to be a reliable measure of walking mobility in PwMS as to internal consistency, test-retest reliability and validity of scores [16]. Measurements were performed at the Center of Advanced Technologies Rehabilitation Center, Sheba Medical Center Tel-Hashomer, Israel.

2.3. Symptomatic fatigue evaluation

The MFIS [17], a self-reported, multidimensional, 21-item questionnaire was used to determine the level of symptomatic fatigue in the MS study group. This instrument captures information related to the effects of fatigue within the physical (9-items), psychosocial (2-items) and cognitive (10-items) domains over a four-week period Participants rated the 21 items on a 5-point Likert-type scale ranging from never (0) to always (4). The MFIS yields three subscale scores and an overall score ranging from 0 to 84.

2.4. Statistics

MS subjects were divided into mild and moderate neurological impaired groups based on the neurological examination and EDSS score. PwMS with scores up to 3 were classified as mildly impaired while those scoring from 3.5 up to 6.5 were classified as moderately impaired. Group differences in age, height, weight, disease duration, MFIS, MSWS-12, EDSS, EDSS functional systems and gender distribution were determined using an independent sample-t and chi-square test, respectively. All spatio-temporal gait data were normally distributed according to the Kolmogorov–Smirnov test. Differences in gait parameters between MS subgroups were determined using an independent *t* test. The magnitudes of group differences were indexed by a 95% confidence interval (95% CI).

In order to determine if gait variables were associated with symptomatic fatigue, the Spearman's rho correlation between MSWS-12, spatiotemporal parameters of gait and MFIS was calculated. Correlation coefficients which were $\leq$0.35 were considered as low or weak correlations, 0.36–0.67 modest or moderate correlations, 0.68 to 0.89 strong or high correlations and $\geq$0.90 very high [18].

In addition, a stepwise multivariate regression analysis was performed on the entire group. Spatio-temporal gait parameters and MSWS-12 were classified as independent variables; the MFIS score was selected as the dependent variable. At each subsequent step, the regression equations comprised those variables reaching specific thresholds of F and P values (for variable inclusion, $F \geq 1$ and $P \leq 0.05$; for exclusion, $F < 1$ and $P > 0.05$). To eliminate redundancy between correlated gait variables, a principal component analysis (PCA) was executed prior to the regression model. This procedure extracted variables carrying the most variance, thus limiting the type I error. The PCA included the Kaiser–Meyer–Olkin measure of sampling adequacy and Bartlett's test of