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The association between multiple sclerosis-related fatigue and balance as a function of central sensory integration

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ABSTRACT

Background: Fatigue and impaired upright postural control (balance) are the two most common complaints in persons with multiple sclerosis (MS), with limited evidence on how they are related.
Objective: To examine the relationship between symptomatic fatigue and balance as a function of central sensory integration in persons with multiple sclerosis.
Materials and methods: Seventeen persons with relapsing-remitting MS were enrolled in this cross-sectional study. Primary measurements included fatigue (modified fatigue impact scale – MFIS); balance (dynamic posturography, sensory organization testing – SOT); and walking capacity (six-minute walk test – 6MWT).
Results: Fatigue scores were significantly associated with balance: MFIS total ($r = -0.78$; $p < 0.001$), physical subscale ($r = -0.77$; $p < 0.001$), cognitive subscale ($r = -0.75$; $p = 0.001$) and psychosocial subscale ($r = -0.53$; $p = 0.030$) scores. MFIS total score was a significant predictor of balance ($p \leq 0.001$), accounting for 62% of the variability in SOT composite scores. Significant differences in fatigue ($d = 1.75$; $p = 0.005$) and balance ($d = 1.74$; $p = 0.005$) were found for participants who had cerebellar and brainstem involvement compared to those without.
Conclusions: Symptomatic fatigue is significantly related to balance and is a significant predictor of balance as a function of central sensory integration in persons with MS. Fatigue and balance are associated with cerebellar and brainstem involvement. This study provides early evidence supporting the theory that for those persons with MS who struggle to maintain steady balance during tasks that stimulate the central sensory integration process, complaints of significant levels of fatigue are probable.

1. Introduction

Multiple sclerosis (MS) is a multi-focal, progressive disorder of the central nervous system (CNS) often resulting in different types of clinical manifestations. Among the possibilities, symptomatic fatigue and impaired upright postural control (balance) offer significant challenges to medical and rehabilitation management of persons with MS. Both of these issues are quite common, with the prevalence of fatigue as high as 85% [1], and impaired balance, up to 87.9% [2]. Collectively, they are main contributors to advanced disability and reasons for poorer quality of life [3], further stressing the importance of these two factors for persons with MS.

Central sensory integration of the visual, somatosensory and vestibular systems is an essential component of effective balance [4,5]. Impairments of the visual [6], somatosensory [7] and peripheral vestibular [8] systems are found in patients with MS, illustrating the likely impact of these sensory impairments on central sensory integration in these individuals. Moreover, persons with MS frequently have involvement in the primary regulators of central sensory integration, namely brainstem and cerebellar regions [9]. Involvement of these areas, and subsequent impaired sensory integration, is a primary reason for postural instability in persons with MS [10]. Furthermore, interruption of the integration process has been found to lead to significant complaints of dizziness and vertigo [9]. Thus, we postulate that for the person with MS who struggles to maintain upright postural stability, due to impaired central integration, would likely suffer from concomitant complaints of fatigue.

The etiology of symptomatic fatigue in persons with MS is not well known, however it is likely multi-factorial [11], having previously been associated with such factors as depression [12],

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and sleep disorders [13]. Recently, the notion that impaired balance and fatigue are interrelated has been studied, with mixed and limited results [14,15]. However, yet to be determined is the relationship between symptomatic fatigue and balance as a function of central sensory integration.

The primary objective of this investigation was to examine the interrelationship of symptomatic fatigue and balance based on computerized, sensory organization (dynamic posturography) testing in persons with MS. Additionally, we aimed to test the association of these two factors with functional system involvement including sensory, pyramidal, cerebellar and brainstem. We hypothesized that symptomatic fatigue would be significantly and inversely related to balance as a function of central sensory integration, and that both fatigue and balance would strongly relate to cerebellar and brainstem involvement.

2. Materials and methods

2.1. Participants

Seventeen participants were recruited and enrolled based on convenience-consecutive sampling through a local Multiple Sclerosis Center. Inclusion criteria were: clinically definite MS confirmed by a board certified Neurologist; able to walk 100 m with or without a single-sided device; between 18 and 60 years of age. Exclusion criteria were: non-ambulatory; use of pharmacological agents to control fatigue; other possible causes of fatigue (including major sleep disorder, clinical depression, anemia, hypothyroidism and B12 deficiency); other disorders which could contribute to significant balance problems (including cerebral vascular accident and peripheral neuropathy); peripheral vestibular disorders (including unilateral/bilateral vestibular hypofunction, benign positional paroxysmal vertigo, Meniere's disease and acoustic neuroma).

2.2. Fatigue assessment

Symptomatic fatigue was measured using the modified fatigue impact scale (MFIS). This questionnaire was modified from the original validated measure of fatigue, the fatigue impact scale [16], by The Consortium of Multiple Sclerosis Centers Health Services Research Subcommittee, for use as a subscale in the multiple sclerosis quality of life inventory (MSQLI). The MFIS is a multidimensional scale designed to assess the perceived impact of fatigue related to different aspects of an individual's daily life. It is a discriminative scale of MS-related fatigue [17] and has been utilized as a measure of MS-related fatigue in previous outcome studies [18]. The MFIS is a 21-item standardized questionnaire. Each item has five levels of response (ranging from 0 to 4). Higher scores report a larger impact of fatigue on the patient's activities. Scores are reported as a total (range: 0–84), or subdivided into three subscales: physical (range: 0–36), cognitive (range: 0–40), and psychosocial (range: 0–8). The MFIS total score and each subscale score was recorded and analyzed.

2.3. Balance assessment

Balance was measured using the SMART Balance Master® (Neurocom® a division of Natus®, Clackamas, OR), a computerized dynamic posturography test/sensory organization test (SOT) [19], which has been used in prior studies to illustrate balance disorders in persons with MS [10,18]. It is designed to systematically assess upright postural control during various conditions of sensory feedback and attempted central sensory integration. The SMART Balance Master® consists of a dynamic force plate situated in the center of a dynamic visual surround, which is monitored electronically. Since the support surface and surround surface are mounted on the same apparatus and calibrated to one another for movement along the same rotational plane (sagittal-anterior and posterior), together they provide accurate measurements of movements as a sway pattern (degrees per second sway). The program consists of six conditions:

(1) Eyes open, no sway reference
(2) Eyes closed, no sway reference
(3) Eyes open, visual/surround sway reference
(4) Eyes open, support surface sway reference
(5) Eyes closed, support surface sway reference
(6) Eyes open, support surface and visual/surround sway reference

Sway reference refers to displacement of the platform and/or the visual surround, which is initiated by sway of the participant and registered as change in center of force on the platform in the sagittal plane. This change in force displacement is converted into a percentage of equilibrium or sway for each of the six conditions. Finally, a composite score of equilibrium is calculated based on the weighted average of the percentage of equilibrium for each condition. Percentage of equilibrium was the unit of measure for the assessment of balance as a function of central sensory integration, and is presented as SOT composite score and as conditions 1, 2, 3, 4, 5 and 6 separately.

2.4. Walking assessment

Walking capacity was measured using the six-minute walk test (6MWT). The 6MWT has been used as a tool to measure functional exercise capacity in the MS population [20]. Standard instructions and testing guidelines were implemented [21]. The location of the test was performed in a level-surface hallway, controlled for possible obstacles and distractions. Each participant was instructed to walk at his/her comfortable, self-selected pace, while traversing 100 foot intervals until the test was completed. Time was recorded using a standard stopwatch. The test was terminated at six minutes. Distance, in feet, was recorded and analyzed.

2.5. Functional system involvement assessment

Identification of each participant's functional system involvement of sensory, pyramidal, cerebellar and brainstem was determined by most recent clinical neurological examination reports conducted by the investigators. These four functional systems were derived from the Kurtzke expanded disability status scale (EDSS) [22]. The EDSS is a 20-point standard measure of disability. Due to the purpose of this study, determination of involvement in the additional functional systems of the EDSS, including vision, cerebral/mental and bowel and bladder were not performed. The presence of clinically determined involvement of these systems was determined as follows: sensory (any limb that had at least impaired light touch, vibration and/or proprioception), pyramidal (any limb that had at least impaired strength and/or spasticity), cerebellar (any limb that had intention tremor or impaired coordination and/or ataxia in trunk in standing or walking) and brainstem (presentation of eye movement dysfunction). Participants were sub-divided into one of two groups based on those with (present) and those without (absent) involvement in the respective functional system, serving as the unit of measurement for this assessment.

2.6. Procedures

A local scientific ethics committee, guided by the ethical principles for human subject research and in accordance with the United States Department of Health and Human Services policy and regulations (45 CFR 46), approved this study. All participants gave written informed consent prior to his/her participation in the study. All measurements were administered by a physical therapist with over 7 years of experience administering the measurements in persons with MS. Testing took place in the morning and each participant underwent all measurements.

2.7. Statistical analysis

The primary variables of fatigue, balance and walking capacity, and measures of age and duration of disease diagnosis were analyzed as continuous data. Gender and each functional system involvement were characterized as nominal data.

To analyze the magnitude and direction of two-variable (bivariate) relationships, Pearson product–moment correlation coefficient was used. Interpretation of the bivariate correlational coefficients was: minimal to no association ($r \leq 0.25$); low to fair association ($r > 0.25$ but ≤ 0.50); moderate to good association ($r > 0.50$ but ≤ 0.75); and good to excellent ($r > 0.75$ but ≤ 1.00) [23].

To investigate what measurements would predict the value of balance, we used stepwise linear regression analysis, with SOT composite score as the dependent variable; all other measures were entered as covariates. The criteria for covariant entry into the final model were set at $p \leq 0.05$ and exclusion from the final model at $p \geq 0.100$. Additionally, measurements that were included in the final model were further analyzed for their contribution to the variability in the primary measurement by squaring the respective correlation coefficient, R-squared (r^2).

The independent t test was used to compare mean values of fatigue and balance based on functional system involvement (present, absent). Two groups were created for each functional system, those who presented with involvement and those who did not. The numeric difference in fatigue (MFIS total score) and balance (SOT composite score) between the groups was determined. Standardized difference of the mean (SDM) was calculated based on Cohen d standard effect size index and presented with the following interpretation: small (d: ≤ 0.2), medium (d: > 0.2 to ≤ 0.7), and large (d: ≥ 0.8–2.0), with 95% confidence intervals (CI) [23,24].

All tests were 2-tailed, using 0.05 as the level of statistical significance. Unless otherwise stated, statistical analyses were performed using SPSS, version 20 for Windows (SPSS, Chicago, IL).

3. Results

3.1. Demographics and characteristics

The description of the study sample, including demographics, characteristics and measurement data are provided in Table 1.