Structural Neural Correlates of Impaired Postural Control in People with Secondary Progressive Multiple Sclerosis

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Background: Secondary progressive multiple sclerosis (SPMS) is characterized by worsening of postural control and brain atrophy. However, little is known about postural deficits and their neuroanatomical correlates in this population. We aimed to determine the neuroanatomical correlates of postural deficits in people with SPMS and whether posture control deteriorates concomitantly with the brain and spinal cord atrophy in 2 years in SPMS.

Methods: This study is a post hoc analysis of data from 27 people with SPMS (mean ± SE age, 58.6 ± 1.1 years). Participants had magnetic resonance imaging (MRI) of the brain and cervical spinal cord followed by sway testing using inertial sensors during standing with eyes open (EO) and eyes closed without (EC) and with (ECC) a cognitive task. Partial correlations investigated relationships between postural control and MRI measures at baseline and 2 years.

Results: At baseline, sway measures were inversely related to cortical thickness and cord cross-sectional area (CSA) during the EO task but only to cord CSA with EC ($P < .05$). After 2 years, the percentage change in sway amplitude and dispersion during EO tasks significantly related to the percentage decline in cord CSA ($P < .01$).

Conclusions: Cortical and spinal cord inputs are essential for regulation of postural control during standing with EO in SPMS. Without visual input, people with SPMS preferentially rely on somatosensory inputs from the spinal cord for maintaining postural control. Postural deficits related to cord atrophy over 2 years, suggesting that postural control may be a surrogate marker of disease progression in people with SPMS. *Int J MS Care*. 2020;22:123-128.

Multiple sclerosis (MS) is a chronic, progressive autoimmune disease of the central nervous system. Most people with MS initially have a relapsing-remitting disease course which is characterized by episodes of acute exacerbation followed by complete or partial recovery.[1,2] Approximately 50% to 60% of people with relapsing-remitting MS (RRMS) progress to secondary progressive MS (SPMS), marked by progressive increase in disability with fewer or no exacerbations.[3,4] Multiple sclerosis is characterized by widespread tissue damage in the white matter of the brain and spinal cord, and the focal lesions in the white matter are the pathologic hallmark of the disease.[5-7] Similarly, gray matter damage is a consistent feature of all MS phenotypes, perceptible from disease onset, and includes focal (ie, cortical lesions) as well as diffuse pathology (ie, atro-

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phy).[8-10] Both white and gray matter changes accumulate over time, causing impaired neurologic functions such as balance (postural control), cognition, vision, muscle tone and strength, sensation, and coordination in people with MS.[11-13]

Balance impairments are a hallmark of MS, from presymptomatic stages to advanced stages of disease progression.[14-21] Traditionally, balance is known to be controlled by the information obtained from the three sensory systems (visual, vestibular, and somatosensory), which can provide a referential context for updating the body's location in extrapersonal space.[15,22-24] Integration of these sensory systems is likely affected by the loss of structural integrity of the brain and spinal cord in people with MS.[25,26] For example, lesions in the spinal cord affecting vestibular and/or somatosensory systems may necessitate greater reliance on the visual system to maintain postural control. However, if visual input is also altered, either due to existing persistent visual impairment in people with MS[27] or by closing their eyes (ie, the Romberg sign),[28] balance problems are amplified. More recent evidence suggests that balance in people with MS can also be negatively affected when a concurrent cognitive task is added.[19,29,30] These studies propose that people with MS require more attentional or processing resources for a single motor task, therefore increasing interference when postural and cognitive tasks are performed simultaneously (cognitive-posture interference). Balance problems are particularly pronounced in people with longer duration and progressive stages of MS, yet most previous studies have investigated balance in only recently diagnosed MS and RRMS phenotypes. Furthermore, very few studies have investigated associated deficits in neuroanatomical structures thought to be related to postural control. The purpose of this study was to investigate the neuroanatomical correlates of postural instability in people with SPMS.

This quantitative physiological and magnetic resonance imaging (MRI) study examined the associations between both cross-sectional and longitudinal changes in postural control and measurements of brain and cervical spinal cord structures. Postural control was measured using inertial sensors during quiet standing under conditions of eyes open (EO), eyes closed (EC), and eyes closed with a cognitive task (ECC). We hypothesized that 1) postural control would worsen in the absence of the visual feedback as well as increased cognitive demands, 2) postural control outcomes would correlate with neuroanatomical structures thought to be related to balance, and 3) worsening of postural control would be associated with atrophy of related neuroanatomical structures over a 2-year period.

Methods

Study Design and Participants

This study is a post hoc analysis of data from the participants recruited for a longitudinal study[31] that was approved by the Veterans Affairs Portland Health Care System (VAPORHCS) and Oregon Health & Science University institutional review boards. Participants were recruited from the MS Center of Excellence clinic at VAPORHCS and from the community. The inclusion criteria were ages 40 to 70 years, diagnosed as having SPMS as defined per the primary paper as "prior RRMS (2005 McDonald criteria), and current SPMS defined by MS disability progression in the absence of clinical relapse during the prior 5 years as determined by the principal investigator (PI) based on history and chart review," Expanded Disability Status Scale (EDSS) score of 6.0 or less, and able to walk at least 25 feet without an aid.[31] People with any other self-reported medical or neurologic conditions that might affect gait (eg, joint replacement, peripheral neuropathy, vestibular disorder, alcoholism, stroke, etc) or interfere with study procedures were excluded. Additional criteria for the post hoc analysis were 1) ability to stand unassisted for 30 seconds during the performance of postural control tests and 2) availability of good-quality data for postural control and brain MRI at baseline. Participants were permitted to start, stop, or continue glatiramer acetate or β-interferon use during the study. The study details were reviewed with the participants, and informed consent was obtained before participation.

Data Collection

Postural Control (ISway Test)

ISway data were captured using a portable motion analysis system that consisted of a body-worn sensor (Opal from APDM Inc, Portland, OR) housing a three-dimensional gyroscope and triaxial accelerometer sampling at 50 Hz (detailed description in a previous article[32]). The sensor was attached on the lumbar trunk at L5 (approximate body center of mass).

Postural control was measured during three balance tasks of increasing complexity: 1) quiet standing with EO, 2) quiet standing with EC, and 3) standing with eyes closed along with the performance of a serial subtraction task by 3s (ECC). Participants were instructed to stand still with arms crossed across the chest, and their feet were positioned by a standardized template block. Three 30-second trials for each balance task were performed. The median of three trials for each balance task was used for data analysis. Measures derived from ISway included sway amplitude (maximum range of the L5 sensor acceleration trajectory), sway dispersion (root mean square [RMS] of the sway trajectory), mean sway velocity (average integral of acceleration trajectory), sway path (total length of the acceleration trajectory), and sway jerk (time derivative of the acceleration and an indicator of the smoothness of postur-

al sway). To reduce risk of type 1 error, we limited the analysis to the previously mentioned sway measures because those have been previously reported to be different in people with MS (mixed types) compared with control participants.[21,33]

Magnetic Resonance Imaging

Structural MRI data were collected on a single 3-T magnet (Philips Achieva 3.0T X-series; in-house: Imaging Department, Portland VA Health Care System) using a 12-channel head coil. Conventional brain MRI with T2-weighted images and fluid-attenuated inversion recovery series (2-mm, non-gapped slice acquisition, in-plane resolution 1 mm^2) were acquired. In addition, a three-dimensional MPRAGE scan for high-resolution structural (T1-weighted) information was obtained. Spinal cord images with sagittal two-dimensional proton-density/T2-weighted sequences were collected. No intravascular MRI contrast was administered.

MRI Data Analysis

The MRI data were processed and analyzed at the Oregon Brain Imaging Research Laboratory in the Portland VA Health Care System by staff/scientists with specific expertise in MS. The detailed MRI data collection and processing procedures are described elsewhere.[31] The five structural measures included in this analysis were white and gray matter volumes, brain cortical thickness, cerebral T2-weighted lesion volume, and average spinal cord cross-sectional area (CSA) measured at the C1 vertebral level.

Statistical Analysis

The nonparametric Wilcoxon signed rank test was used for within-subject comparisons of balance task performance under three different conditions (EO vs EC, EO vs ECC, and EC vs ECC), and the results were corrected for multiple comparisons. Spearman partial correlations in IBM SPSS Statistics for Windows, version 21.0 (IBM Corp, Armonk, NY) were used to investigate the relationship between postural control and brain measures after controlling for the effect of age. For longitudinal analysis, the partial correlations (controlled for age) were used to examine the relationships between percentage change in sway and brain measures that were found to be significant at baseline.

Results

Demographics

Twenty-seven people with SPMS (11 men and 16 women) were included in the present analysis, with a mean ± SE age of 58.6 ± 1.1 years at baseline. The median EDSS score of people with SPMS was 4.5 (range, 3.0-6.5). The baseline characteristics of the study participants are given in Table S1, which is published in the online version of this article at ijmsc.org.

Cross-sectional Analysis

Postural Control (ISway)

People with SPMS demonstrated a significant increase in the sway measures RMS, Range, Jerk, and Path during the EC and ECC conditions compared with balance task performance with EO, indicating worsening of postural control during the former tasks (Figure 1). However, no statistically significant differences were seen in sway measures between EC and ECC balance task performance.

MRI Findings and Associations with ISway

Cortical thickness was negatively associated with all four sway measures (Jerk, Path, RMS, and Range) during the EO balance task, indicating that smaller cortical thickness is related to greater sway and, hence, poor postural control during standing with EO (Table 1). Similarly, spinal cord CSA was negatively associated with the sway measures RMS and Range during EO balance task performance, with smaller spinal cord area related to larger postural sway. However, during the EC

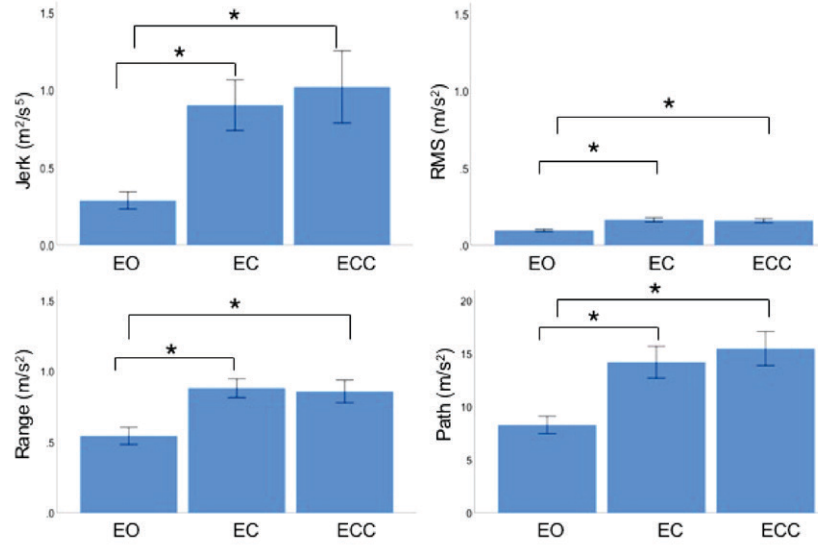

Figure 1. **People with secondary progressive multiple sclerosis showed significant increases in root mean square (RMS), Range, Jerk, and Path with eyes closed (EC) and during dual-task performance with eyes closed and a cognitive task (ECC) compared with quiet standing with eyes open (EO)**

There were no significant differences between EC and ECC conditions. *$P < .05$ (corrected for multiple comparisons).

Table 1. **Relationship between postural sway measures and structural brain measures (controlled for age) at baseline in people with secondary progressive multiple sclerosis**

Condition and measure	Spearman correlation *r*				
	Gray matter volume	White matter volume	Cortical thickness	Spinal cord CSA	T2 lesion volume
EO					
Jerk	–0.13	–0.18	–0.42[a]	–0.33	0.23
RMS	–0.14	0.02	–0.63[a]	–0.61[a]	0.33
Range	–0.10	0.01	–0.64[a]	–0.64[a]	0.26
Path	–0.16	–0.04	–0.45[a]	–0.34	0.20
EC					
Jerk	0.08	0.10	–0.30	–0.32	–0.07
RMS	–0.08	0.22	–0.40	–0.43[a]	–0.07
Range	0.05	0.17	–0.30	–0.43[a]	–0.18
Path	0.06	0.20	–0.32	–0.30	–0.11
ECC					
Jerk	–0.18	–0.01	–0.32	–0.14	0.13
RMS	0.12	0.14	–0.20	–0.08	0.02
Range	0.05	0.04	–0.27	–0.15	0.04
Path	–0.24	0.03	–0.37	–0.14	0.13

Abbreviations: CSA, cross-sectional area; EC, eyes closed; ECC, eyes closed with cognitive task; EO, eyes open; RMS, root mean square.
[a]$P < .05$.

balance task, only cord CSA was significantly associated with the postural sway measures RMS and Range. No associations were found between structural brain and sway measures during the dual-task ECC balance test performance. Furthermore, white matter volume, gray matter volume, and cerebral T2 lesion volume were not associated with any postural sway measure during EO, EC, or ECC balance tasks. The results of the average structural measures of brain and spinal cord are summarized in Table S2.

Longitudinal Comparisons

Of the 27 original participants with SPMS who could stand independently in all three sensory conditions at baseline, only 19 (70%) were able to complete ISway testing during the EO balance task, and only 17 (63%) were able to complete sway testing during the EC and ECC balance tasks after 2 years. We found that percentage change in the postural sway measure RMS and Range were inversely related to the percentage decline in spinal cord CSA after 2 years during balance task performance with EO but not with the EC condition (partial data, Table 2; complete data, Table S3). We did not find significant relationships between changes in cortical thickness and sway measures during either EO or EC balance task performance. In a post hoc analysis, dalfampridine use (n = 12) did not affect study outcomes.

Table 2. **Relationship between longitudinal changes in postural sway measures and structural brain measures (controlled for age) after 2 years in people with secondary progressive multiple sclerosis**

	Spearman correlation *r*	
	Change in spinal cord CSA (%)	Change in cortical thickness (%)
Change in EO RMS (%)	–0.72[a]	0.37
Change in EO Range (%)	–0.73[a]	0.22
Change in EC RMS (%)	–0.07	–0.31
Change in EC Range (%)	0.24	–0.14

Abbreviations: CSA, cross-sectional area; EC, eyes closed; EO, eyes open; RMS, root mean square.
[a]$P < .05$.

Discussion

A key finding of this study was that postural sway measures were related to cortical thickness and spinal cord CSA in people with SPMS when standing with EO. In contrast, postural sway measures (RMS and Range) were related only to spinal cord CSA after visual input was removed. In addition, the percentage change in the sway measures RMS and Range in the EO condition significantly reflected the percentage decline in spinal cord CSA after 2 years. This relationship suggests that postural sway may be a sensitive indicator of spinal cord atrophy in people with SPMS.

The present investigation reinforces the significance of the Romberg sign in people with SPMS by demonstrating a significant increase in postural sway after visual input was removed and adds new information on postural sway's neuroanatomical correlates. The association between spinal cord atrophy and postural instability has been demonstrated by a previous study.[34] Similar to the present findings, Prosperini et al[34] reported that EC standing balance was inversely related to the upper cervical cord CSA. Although in the previous study balance control in the EC condition was also related to the abnormalities of other neuroanatomical structures, including the midsagittal cerebellum area and lesion volumes at the infratentorial level, the multivariable regression analyses revealed that the spinal cord atrophy had the strongest association with the EC standing balance task. Collectively, these results corroborate a shift of dependence on somatosensory input (proprioception) for the regulation of postural control in the absence of

visual information, consistent with the models of sensory integration for postural control.[35,36]

To our knowledge, this is the first study to demonstrate that MS-related spinal cord atrophy mirrors the decline in postural sway over time in people with SPMS. We would expect this association because cord-specific abnormalities have been reported to cause balance and sensorimotor dysfunction in people with MS. Loss of spinal cord CSA could reflect both slowed and reduced afferent proprioceptive conduction along dorsal columns of the spinal cord and/or slowed and reduced corticospinal motor control due to damage to cord integrity.[25,37,38] With the addition of data from the present study, these findings emphasize the primary role of spinal cord contributions to MS-related balance deficits. Importantly, the finding of the association between spinal cord CSA atrophy and postural instability over time indicates that balance might be used as an outcome measure for monitoring the effects of neurorestorative therapies aimed at reducing brain and spinal cord atrophy.

Contrary to our expectations of further deterioration of postural control during the ECC balance task compared with the EC task, we did not find an additional impact of cognitive loading on postural control in this cohort. This may be due to the study design that did not test postural control during cognitive task performance with EO. As one of the most critical sensory information systems for postural control,[39-41] the relative impact of the cognitive task may have simply been overshadowed by the effects of the visual loss. Another possibility is that the subtraction arithmetic task was too simple a challenge for cognitive loading and, hence, insufficient for further deterioration of postural control in the present cohort. Other studies have indicated that the impact of dual-task interference is most visible with complex secondary tasks.[42] Thus, future studies evaluating the influence of cognitive loading on postural balance control should use a more complex dual-task performance with and without visual feedback to determine the differential effects of this challenge.

Notably, after 2 years of disease progression, the percentage change in spinal cord thickness in people with SPMS was related only to postural sway changes in the EO condition but not in the EC condition. We attribute this lack of relationship partially to the relatively lower number of participants who were able to perform the postural sway task with EC at 2 years (17 of 27 original participants). Another possibility is that after 2 years of disease progression, people with SPMS would have relied more heavily on the vestibular system in the absence of the visual input than on the somatosensory feedback because the latter must have been too delayed to adequately allow individuals with progressive phenotype to depend on somatosensation for successful balance control.[38] Although suggestive, this hypothesis needs confirmation in future longitudinal studies with sufficient power.

The main purpose of this study was to explore the neuroanatomical correlates of postural instability in people with SPMS, which could be subject to more rigorous future examination. Specifically, at baseline, 60 comparisons were made among sway and MRI measures without correcting for multiple comparisons because statistical power was deemed to be insufficient. Therefore, the correlation findings from this exploratory analysis should be regarded as preliminary unless rigorously tested and replicated in future studies. In addition to the issues surrounding the lower sample size, other limitations of this study include the lack of comparison groups (healthy controls or people with RRMS). Furthermore, we did not directly test the elements of spinal cord inputs (sensation, proprioception, spinocerebellar and vestibular function, etc) to determine which were contributing to impaired postural control and spinal cord atrophy. Cerebellar function and volumes were also not evaluated in the present study. In addition, the specific contribution of the visual cortex, as opposed to the averaged whole-brain cortical thickness, was not explored. Adding these elements to future study designs will result in a more robust determination of the factors resulting in balance problems in people with progressive MS.

In summary, this study demonstrated that when visual, vestibular, and somatosensory inputs were available, cortical thickness and spinal cord CSA were related

PRACTICE POINTS

- With eyes open, cortical thickness and spinal cord cross-sectional area (CSA) relate to postural deficits in people with secondary progressive multiple sclerosis.
- With eyes closed, only spinal cord CSA relates to postural control, as expected from the Romberg test.
- In 2 years, the spinal cord CSA atrophies in tandem with deterioration in postural control.

to postural deficits in people with SPMS, whereas spinal cord atrophy was the only anatomical correlate of poor postural control while standing with EC. Deterioration of postural sway with EO and C1 spinal cord CSA atrophy over 2 years were also related, suggesting that balance testing might serve as a marker of repair for future neurorestorative therapies. □

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