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Spinal cord dysfunction contributes to balance impairment in multiple sclerosis patients

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ABSTRACT

Objectives: Balance impairment is very common in multiple sclerosis (MS) but its causes are still unclear. Some studies suggest that balance deficit originates mainly from damage in specific locations of the central nervous system such as cerebellum and spinal cord, that are involved in transmission and integration of sensory inputs and motor outputs. The aim of this study is to investigate the contribution of spinal cord to MS-related imbalance, by combining neurophysiologic and neuroimaging techniques.

Patients and methods: Balance performance was correlated with clinical, neurophysiological and MRI findings. The functionality of spinal cord was tested by somatosensory (SEP) and motor (MEP) evoked potentials. MRI was used to identify spinal and cerebellar lesions. Balance performance was assessed by Tinetti Scale (TS). Clinical disability was measured by EDSS.

Results: 38 patients were included. Linear regression model revealed significant negative correlations between TS and EDSS scores, between TS and cervical lesions, and between TS and SEP findings.

Conclusion: Our study, by combining neurophysiologic and neuroimaging techniques, confirms that spinal cord plays an important role for balance control and that its dysfunction, especially in lower limbs somatosensory ascending pathways conveying proprioceptive information, contributes to balance impairment in MS patients.

1. Introduction

Balance impairment is very common among people with multiple sclerosis (MS), and it has a deep impact on their disability and quality of life. Indeed, imbalance affects gait and significantly increases the risk of fall [1]. Balance disorders can affect MS patients all along the natural history of the disease. In fact, imbalance does not only involve patients with advanced disease and significant disability [1], but it is often an early symptom affecting patients with minimal or no disability [2]. Although balance problems are so widespread in MS patients, their causes are still unclear [3]. MS can involve different regions in the central nervous system (CNS) potentially related to balance, such as visual, vestibular, motor, sensory, cognitive, and cerebellar pathways [4,5]. However, magnetic resonance imaging (MRI) studies suggest that balance deficit mainly originates from damage in specific locations of CNS such as cerebellum [6] and spinal cord [7]. These areas are involved in the central mechanisms of transmission and integration of sensory inputs and motor outputs [8]. According to a traditional view, the involvement of cerebellum and its connections is the primary contributor to the balance impairment [9]. However, more recently, converging evidence from both neurophysiological [10] and neuroimaging studies [7,11] have demonstrated that also spinal cord plays an important role in balance control. Through spinal columns, proprioceptive information is conveyed from peripheral receptors to the cortex, and motor signals are transmitted from the motor cortex to muscles. Sensorimotor conduction, in particular at the spinal level, cannot be adequately addressed exclusively by conventional structural MRI, and it rather requires functional assessment that can be provided by neurophysiologic techniques [12]. MRI is an insuperable tool to detect MS lesions and it also allows to examine some mechanisms of damage through advanced techniques. However, these techniques are time-demanding, expensive, and with some limitations in the study of the spinal cord and in the assessment of functional connectivity, especially between distant areas. In this context, a useful support could be provided by neurophysiologic techniques such as evoked potentials (EPs). Despite the advent of MRI greatly reduced the use of EPs in the overall

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diagnosis of MS, their role remains primarily stable in the functional evaluation of specific pathways such as visual, somatosensory, auditory, and motor systems and in the study of central mechanisms of sensorimotor transmission and integration [13].

Rehabilitation is the main option for the treatment of MS-related unbalance and several strategies have been proposed, including proprioceptive exercises [14], motor [15] and sensory training [16], and vestibular rehabilitation [17]. A better understanding of the causes of balance impairment could be useful to design customised rehabilitation for MS patients, based on the identification and the training of the most impaired pathway (visual, vestibular, motor, sensory, cerebellar) of each patient.

The aim of this study is to evaluate the causes of imbalance in people with MS. In particular, we have investigated the contribution of spinal cord for balance performance by combining neurophysiological and neuroimaging techniques. To this purpose, in a sample of 38 MS patients, balance performance has been correlated with clinical, neurophysiological and MRI findings.

2. Material and methods

This study involved patients attending the MS center at "Policlinico Campus Bio-Medico di Roma" between January 2015 and December 2017. The potential participants to the study have been selected by a review of the electronic database of our MS center, according to the following criteria:

Inclusion criteria:

- Diagnosis of MS according to the 2010 Revised McDonald Criteria [18];
- Clinical, neurophysiological, and MRI evaluation at our MS center during the selected period (January 2015–December 2017);
- MRI and neurophysiologic tests performed within 1 month from clinical evaluation.

Exclusion criteria:

- Absence of recordable responses at somatosensory evoked potentials (SEP) and motor evoked potentials (MEP), not allowing to calculate central somatosensory and/ or conduction time.

The study was approved by the Local Ethical Committee.

All subjects had a complete clinical neurological evaluation. The Expanded Disability Status Scale (EDSS) was used to measure clinical disability. Balance was assessed by the balance component of Tinetti Scale (TS). The TS is a simple, easily administered test that measures gait and balance. The balance component of TS is composed of 9 items and the maximum score (indicating normal balance) is 16 points. Scoring is done on a three point ordinal scale with a range of 0–2 (0–1 for items 1 and 6): 0 represents the most impairment, while 2 represents independence [19]. Both EDSS and TS were administered by trained neurologists.

The functionality of central somatosensory and motor pathways was tested by SEP and MEP, respectively. SEPs were examined bilaterally from both hands (median nerve) and feet (tibial nerve) [20]. Electric stimuli were delivered at a rate of 5 Hz at motor threshold intensity, at the wrist for median nerve and at the ankle for tibial nerve. Two averages of 1000 trials for each nerve were obtained. For median nerve SEP recording, the electrodes were placed at the Erb's point (referred to Fz), over the spinous process of the 6th cervical vertebra (referred to an electrode located immediately above the thyroid cartilage) and at the contralateral and ipsilateral parietal scalp regions (referred to ear lobe ipsilateral to the stimulated side). We recorded the N13 potential (generated in the cervical spine), the P14 potential (generated in the medial lemniscus above the foramen magnum), and the N20 potential (generated in the parietal cortex). Moreover, to assess conduction in the intracranial segment of the somatosensory pathway, we measured the P14-N20 interpeak latency. For tibial nerve SEP, the recording electrodes were placed over the spinous process of the 12th thoracic vertebra (referred to the anterior abdomen) and at the vertex (referred to Fz). We recorded the N24 potential (generated in the spine at Th12 level), and the P40 potential (generated in the cortex). In order to evaluate the central somatosensory conduction, we measured the N24 - P40 interpeak interval. Total central somatosensory conduction time (CSCT = P40 latency – N24 latency) was divided into cranial (CSCTcr = N20 latency – P14 latency) and spinal (CSCTsp = CSCT - CSCTcr) components [10]. CSCT, CSCTsp, and CSCTcr were calculated for right and left side, separately.

Central motor conduction was evaluated using magnetic stimulation of the motor cortex and spine [20]. A Magstim 200 stimulator (Magstim, Whitland, UK) was used to deliver transcranial and lumbar paravertebral magnetic stimuli through a 120 mm circular coil. MEPs were recorded from abductor allucis muscles of both sides by surface electrodes. For each side, three MEPs were recorded after paravertebral stimulation and five MEPs after transcranial stimulation. In both cases, the shortest latency was measured. Central motor conduction time (CMCT) to lower limbs was evaluated by subtracting the latency after lumbar stimulation from the latency after cortical stimulation during voluntary contraction of the target muscles. CMCT was calculated for right and left side, separately.

A standardized MRI protocol was not used, as this was a retrospective study based on scans performed for clinical practice. All MRI examinations were obtained on 1.5 MR scanner. Minimum protocol for the inclusion in the study required the following sequences: for the brain scans, T1-weighted sequences and T2-weighted or FLAIR sequences in at least two orthogonal planes; for the spinal cord scans, T1-weighted sequences and sagittal (and, when available, axial) T2-weighted sequences. The slice thickness had to be no more than 5 mm [21]. Lesions were identified on FLAIR sequences. In particular, we focused on spinal (presence/absence, location) and cerebellar (presence/absence) lesions.

MRI and neurophysiologic tests were performed within 1 month from clinical evaluation.

2.1. Statistics

Linear regression model with robust standard errors of TS on EPs parameters (CMCT and CSCT) was employed, controlling for other covariates (gender, age, EDSS, presence of spinal lesions at MRI) that, according to literature [8], could influence postural stability. They were classified in the following way: cervical MRI takes value 1 in patients with cervical lesions; dorsal MRI takes value 1 in patients with dorsal lesions; cervical & dorsal MRI takes value 1 in patients showing at the same time both a cervical lesion and dorsal lesion; cerebellar MRI takes value 1 in patients with cerebellar lesions. CMCT values obtained from both sides were averaged for each subject and this measure was considered in the analysis. The same method was used for CSCT. Moreover, CSCT was evaluated either as total conduction time or decomposed into CSCTsp and CSCTcr.

3. Results

38 patients (15 male, mean age: 42.7) affected by MS (36 relapsing-remitting and 2 progressive) were included. The median EDSS score was 2.5. 18 patients (47%) had balance impairment (TS score < 16). Regarding neurophysiological study, CSCT was abnormal in 16 patients (42.1%) and CMCT in 14 patients (36.8%) (Table 1). Mean CSCT was 19 ms (± 4.13) on right side and 19.9 ms (± 4.27) on left side. Mean CMCT was 14.2 ms (± 3.94) on right side and 15.6 ms (± 4.19) on left side.

MRI revealed spinal cord lesions in 30 patients (78.9%) and cerebellar lesions in 13 patients (34.2%). Among patients with spinal cord

Table 1
Clinical, Neurophysiological, and MRI findings.

Gender [M] (% male)	15	(39,4%)
Age [mean] (± SD)	42.7	(± 14.5)
EDSS [median] (range)	2.5	(0–6.5)
Tinetti score [mean] (± SD)	14	(± 2.96)
Spinal cord lesion (%)	30	(78.9%)
Cervical spinal cord lesions (%)	14	(36.8%)
Dorsal spinal cord lesions (%)	3	(7.9%)
Cervical & dorsal spinal cord lesions (%)	13	(34.2%)
Cerebellar lesions (%)	13	(34.3%)
Abnormal CSCT (%)	16	(42.1%)
Abnormal CMCT (%)	14	(36.8%)

SD: standard deviation; EDSS: Expanded Disability Status Scale; CSCT: lower limbs central somatosensory conduction time; CMCT: lower limbs central motor conduction time. Abnormal lower limbs CSCT: > 20 ms; Abnormal lower limbs CMCT: > 18 ms.

Table 2
Linear regression model of Tinetti Scale on EPs parameters and control variables.

Variable	Model 1	Model 2	Model 3	Model 4
Gender (M = 1)	0.0656	0.1706		
	(0.6757)	(0.6863)		
Age	−0.0168	−0.0225		
	(0.0233)	(0.0249)		
EDSS	−1.1924**	−1.1598**	−1.2399**	−1.2199**
	(0.2439)	(0.2439)	(0.2929)	(0.2778)
Cervical MRI	−1.8707*	−1.8808*	−1.5805**	−1.5481*
	(0.8281)	(0.8494)	(0.5456)	(0.5693)
Dorsal MRI	−1.7046	−1.7323		
	(1.6666)	(1.6999)		
Cervical & Dorsal MRI	0.6216	0.4938		
	(0.9098)	(0.9012)		
Cerebellar MRI	−1.1532	−1.1037		
	(0.7432)	(0.738)		
CMCT	−0.1474	−0.1533		
	(0.1153)	(0.1194)		
CSCT	−0.2076*		−0.2567**	
	(0.0885)		(0.078)	
CSCTcr		−0.0732		
		(0.2481)		
CSCTsp		−0.2033*		−0.2532**
		(0.0911)		(0.0748)
Constant	24.938**	24.526**	22.597**	21.356**
	(1.6888)	(1.8069)	(1.5711)	(1.221)
F-test	$F_{9,28} = 6.31$**	$F_{10,27} = 5.45$**	$F_{3,34} = 11.77$**	$F_{3,34} = 12.17$**
R^2	0.7499	0.7511	0.6537	0.6484
N	38	38	38	38

Notes: Robust standard errors in parentheses.
**: p < 0.01; *: p < 0.05; EDSS: Expanded Disability Status Scale; MRI: Magnetic Resonance Imaging; CMCT: central motor conduction time; CSCTcr: central somatosensory conduction time, cranial component; CSCTsp: central somatosensory conduction time, spinal component.

involvement, 14 patient had lesions in cervical spine, 3 patients had lesions in dorsal spine, and 13 patients had both cervical and dorsal lesions.

Linear regression model (Table 2, Model 1) revealed a significant negative correlations between TS and EDSS scores ($p < 0.01$), between TS and cervical lesions ($p < 0.05$), and between TS and total CSCT at SEP ($p < 0.05$). Further analysis conducted by decomposing CSCT into CSCTsp and CSCTcr (Table 2, Model 2), confirmed the results, showing that there is a significant negative correlation between TS and CSCTsp ($p < 0.05$), but not between TS and CSCTcr. The small sample size and the relative high number of explanatory variables raise concerns of potential multicollinearity and model overfitting. To deal with the first issue, we computed the variance inflation factor (VIF). In both models, multicollinearity is not a concern: the mean VIF is 1.84 in Model 1 and 1.96 in Model 2, and all VIF values are well below 4. To deal with the overfitting issue, we estimated again our models, by removing all variables that were not significant in Model 1 (Model 3) and Model 2 (Model 4). Results show minimal changes in the values of coefficients and confirm or reinforce the statistical significance of the correlations emerging from Model 1 and Model 2.

4. Discussion

In this study, we have evaluated, by means of EPs and MRI, the contribution of spinal cord to balance performance in MS patients.

Our study confirms that balance impairment is common among MS people (47% in our sample), also in the initial stages of disease when the level of disability is low (median EDSS in our sample = 2.5). However, as expected, unbalance becomes more common among patients with higher disability levels. Indeed, statistical analysis revealed a significant, negative correlation between TS and EDSS scores ($p < 0.01$).

Regarding neurophysiologic tests, linear regression model revealed that TS was significantly correlated with SEP findings. Lower limbs SEP explore the functionality of the ascending sensory pathways conveying proprioceptive information from the peripheral receptors to the cortex through the sensory nerve fibers, posterior columns of the spinal cord, medial lemniscus and the ventral posterolateral thalamic nuclei. In particular, we found that MS patients with poorer balance performance (lower TS scores) have a delayed central sensory conduction (longer CSCT values). Such delay depends on a spinal dysfunction because we found that TS score correlates with CSCTsp rather than CSCTcr (see Table 2). Our results confirm previous evidence that sensory afferent pathway is very important for postural control and gait and its dysfunction is involved in the pathogenesis of MS-related postural instability. In particular, proprioceptive impairment in the lower limbs is very common and represents an independent predictor of balance limitation [22]. Moreover, Cameron et al. [10], found that MS people, compared to controls, have delayed postural responses that are correlated with the latencies of their spinal SEP and, Chinnadurai et al. [23] demonstrated that lower limbs CSCT is also correlated with the risk of falls.

We also examined the functionality of motor system by MEP. We did not find any correlation between TS and CMCT. Thus, our data suggest that, in MS patients, afferent proprioceptive pathway could be more relevant than efferent motor pathway for balance control. These findings are partially surprising because it has been previously demonstrated that primary motor cortex contributes to the postural control in healthy subjects [24], and motor dysfunction reduces stability and increases tendency to fall in MS patients [25,26]. The discrepancies between our findings and literature data about the role of motor system for balance maintaining in MS people could be due to different reasons. First, we used MEP for evaluating the functionality of corticospinal system while other studies exclusively relayed on clinical scales such EDSS. It is reasonable to hypothesize that neurophysiology is more specific and accurate than clinical examination in identifying dysfunction of lateral and anterior corticospinal tracts. Second, since the multifactorial nature of postural instability in MS patients and the reduced size of our sample, it is possible that we included a low number of patients with balance impairment related to motor dysfunction.

MRI findings confirmed the results of neurophysiological tests showing that spinal involvement is correlated with balance performance in MS patients. Indeed, linear regression model revealed a significant negative correlation between TS and cervical lesions ($p < 0.05$). The role of cervical spine for postural control has been ascertained in several studies. Zackowski et al. [7] examined 42 MS patients using magnetization-transfer-weighted MRI to quantify damage of cervical spinal white matter columns and tested its association

with sensorimotor impairment. They found that spinal cord signal measures correlated with walking and balance dysfunction. These results were later confirmed and expanded by Oh et al. [27] in a large, heterogeneous MS sample. Multiple quantitative MRI indices evaluating atrophy and microstructure of cervical spinal cord demonstrated independent associations with lower limbs sensorimotor dysfunction.

Although, several studies have demonstrated that cerebellum has a primary role in MS-related postural instability [5,6], and, in our sample, cerebellar lesions at MRI were relatively frequent (34.2%), we did not find any significant correlation between TS and the presence/absence of cerebellar lesions. However, this is not surprising because other studies have demonstrated that even though both cerebellum and spinal cord are associated with impaired balance in MS, the contribution of these structures can differ among different patients or clinical conditions [10,11]. In particular, Prosperini et al. [11] suggested that the role of spinal cord become prominent when visual input fails and there is a greater reliance on other sensory systems, such as proprioceptive input.

Our study has a number of limitations. First, this study was conducted on a small sample size with some important selection bias such as the exclusion of patients without recordable responses at SEP or MEP. Second, balance deficit has been quantified only by means of clinical scales (TS) without using more objective tools such as posturographic techniques. Third, for the evaluation of motor system and its contribution to balance control, we only considered conduction parameters such as CMCT. Thus, we cannot rule out that different measures of corticospinal and intracortical excitability such as MEP amplitude, short-interval intracortical inhibition (SICI) and facilitation (ICF) could be related to balance performance as already demonstrated in healthy subjects [28]. Finally, the lack of correlation between balance performance and the cerebellar involvement at MRI should be considered with great caution because we exclusively focused on the presence/absence of T2 lesions in cerebellum. Indeed, the role of damage of cerebellar structures and connections in determining balance impairment has been emphasized in several studies that have used different MRI modalities and methods of analysis (atrophy, diffusion tensor imaging, etc) to examine cerebellum [29,9].

5. Conclusions

Our study, by combining neurophysiologic and neuroimaging techniques, confirms that spinal cord plays an important role for balance control and its dysfunction, especially in lower limbs somatosensory ascending pathways conveying proprioceptive information, contributes to balance impairment in MS patients. Moreover, our data suggest that, in MS patients, afferent proprioceptive pathway could be more relevant than efferent motor pathway for balance control. These findings, by providing a better understanding of the causes of MS-related balance impairment, may also have a practical utility for rehabilitation. Indeed, they suggest that improving balance along with strength, endurance, and motor performance may lead to better outcomes in people with MS. In broader terms, since MS-related balance disturbance has a multifactorial origin (visual, vestibular, motor, sensory, cognitive, cerebellar dysfunction) [8] and specific exercises targeting balance can improve performance also in MS individuals with significant disability [30], the use of neurophysiologic tools such as SEP, MEP, VEP, and Vestibular Evoked Myogenic Potentials (VEMP) could be useful, in the single patient, to identify the most impaired pathway and, thus, the most appropriate rehabilitation strategy [13].

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Declaration of Competing Interest

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