Motor and respiratory functions are main challenges to patients with multiple sclerosis

Funções motoras e respiratórias representam desafios importantes para pacientes com esclerose múltipla

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Abstract

Introduction: People with multiple sclerosis (MS) present wide and varied symptoms. **Objective:** To investigate the impact of MS on subjects' motor and respiratory functions. **Methods:** One hundred one participants were enrolled in this study. The subjects had previous diagnosis of relapsing-remittent MS (n = 48) or presented no neurologic diseases (n = 53, control group). Assessments involved mobility (Timed Get Up and Go) and balance (Berg Balance Scale) tests. A force platform was used to evaluate postural stabilometry. Respiratory functions were assessed with a portable spirometer and a digital manovacuometer. Data analyses were carried out with Student´s t-tests, chi-square, and Pearson correlation index. Significance was set at 5%. **Results:** Compared to control peers, participants with MS showed higher motor dysfunctions affecting mobility, balance, and postural stability. Spirometry indicated normal parameters for pulmonary flows and lung capacities in both groups. The manovacuometer, differently, pointed to a respiratory muscle weakness in 48% of participants with MS. Correlation analyses highlighted that respiratory functions are more associated to dynamic than to static motor tests. **Conclusion:** Pathological changes in MS lead to motor dysfunction on mobility, balance and postural stability. Respiratory tests showed normal pulmonary flows and lung capacities in patients with MS, but with commitment of respiratory muscle strength. Respiratory functions were more impacted by dynamic tasks rather than static motor tasks.

Keywords: Motor activity. Multiple sclerosis. Respiratory function tests. Spirometry.

Resumo

Introdução: *Pessoas com esclerose múltipla (EM) apresentam sintomas amplos e variados.* ***Objetivo:*** *Investigar o impacto causado pela EM nas funções motoras e respiratórias.* ***Métodos:*** *Cento e um participantes foram incluídos neste estudo. Os sujeitos tinham diagnóstico prévio de EM remitente-recorrente (n = 48) ou não apresentavam doenças neurológicas (n = 53, grupo controle). As avaliações envolveram testes de mobilidade (Timed Get Up and Go) e equilíbrio (Berg Balance Scale). Uma plataforma de força foi utilizada para avaliar a estabilometria postural dos sujeitos. As funções respiratórias foram avaliadas com um espirômetro portátil e um manovacuômetro digital. A análise dos dados foi realizada pelos testes t de Student, qui-quadrado e pelo índice de correlação de Pearson. Nível de significância foi estipulado em 5%.* ***Resultados:*** *Comparados com controles saudáveis, participantes com EM apresentaram maiores disfunções motoras que afetam mobilidade, equilíbrio e estabilidade postural. A espirometria indicou parâmetros normais para fluxos pulmonares e capacidades pulmonares em ambos os grupos. A manovacuômetria, diferentemente, apontou fraqueza dos músculos respiratórios em 48% dos participantes com EM. Análises de correlação destacaram que as funções respiratórias estão mais associadas a testes motores dinâmicos do que a testes estáticos.* ***Conclusão:*** *As alterações patológicas na EM levam à disfunção motora na mobilidade, no equilíbrio e na estabilidade postural. Os testes respiratórios mostraram padrões normais para fluxos pulmonares e capacidades pulmonares em pacientes com EM, mas com comprometimento da força muscular respiratória. As funções respiratórias foram mais afetadas por tarefas motoras dinâmicas do que por tarefas estáticas.*

Palavras-chave: *Atividade motora. Esclerose múltipla. Testes de função respiratória. Espirometria.*

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune and demyelinating disease that affects the white matter of the central nervous system. The disease is characterized by lesions in the myelin sheath of neurons, resulting in a slow nerve conduction.[1,2] Depending on the location of lesions, a wide range of neurological symptoms arises and affects patients' everyday life.

Among all symptoms seen in MS, motor signs stand out because of its impact on subjects' independence.[3] Balance disturbance, mobility problems and postural instability are some of the symptoms seem in MS.[4-6]

The physiological mechanism related to motor dysfunctions is associated to an inaccurate stimulus on patients' cortex that end up delaying motor actions and reactions.[7] As consequence, patients are subject to a greater risk of falls and many of them start using assistive devices (such as bracing, walking sticks, and wheelchairs) for safety.[8]

Another factor associated to disability in MS is the commitment of the respiratory system. Previous studies reported respiratory dysfunctions in MS and its association to perceived fatigue, physical endurance and quality of life.[9-12] The commitment of the respiratory system is consequence of the presence of demyelinating plaques on patients' brainstem, and it usually occurs in the later stage of the disease.

In spite of previous studies showing commitment of motor and respiratory functions in MS, the large number of confounding variables and the lack of standardization makes the understanding of the clinical condition challenging. Furthermore, until the present moment no study has provided complementary analyses associating motor and respiratory functions in MS.

In this scenario, we performed an in-depth analysis aiming to investigate the impact of MS on motor and respiratory functions, and to verify how motor and respiratory variables affect each other. A control group was included to compare results of subjects with and without MS.

We believe the finding of this study may guide physical therapists and other health care professionals during patient's treatment as it brings news information about the impact of pathological changes in MS.

Methods

This is a cross-sectional design study comprised by two groups: MS and control. The MS group was formed by individuals with relapsing remittent MS. The control group was formed by subjects without MS, but with similar sociodemographic characteristics (age, sex, schooling, weight, height, and body mass index) to the MS group. This research was conducted in accordance

to the Declaration of Helsinki and it was approved by the institutional Ethics Committee (Universidade Federal de Mato Grosso do Sul, protocol No. 2.879.787, CAAE: 89594818.2.0000.0021). All participants provided written consent prior the assessments.

Inclusion criteria involved participants with and without relapsing remittent MS, of both sexes, aged 18 or more. A neurologist with experience in demyelinating diseases performed the diagnosis of the MS group. Exclusion criteria of both groups were participants unable to understand the tests, cases of mental confusion or cognitive decline, presence of comorbidities in lower limbs, smoking history, previous respiratory diseases, pregnancy, and subjects with routine activities superior to three metabolic equivalents of task.[13] The use of walking aids, wheelchairs and patients bedridden were also reasons for exclusion.

Methodological procedures

All methodological procedures are reported according to the STROBE statement checklist. The software G*Power® was used for sample size calculation. Authors analyzed previous studies involving mobility, balance, and respiratory functions in MS,[14-16] and found that the minimal number of subjects should be of 94 participants – 47 per group. Figure 1 details the flow of participant selection.

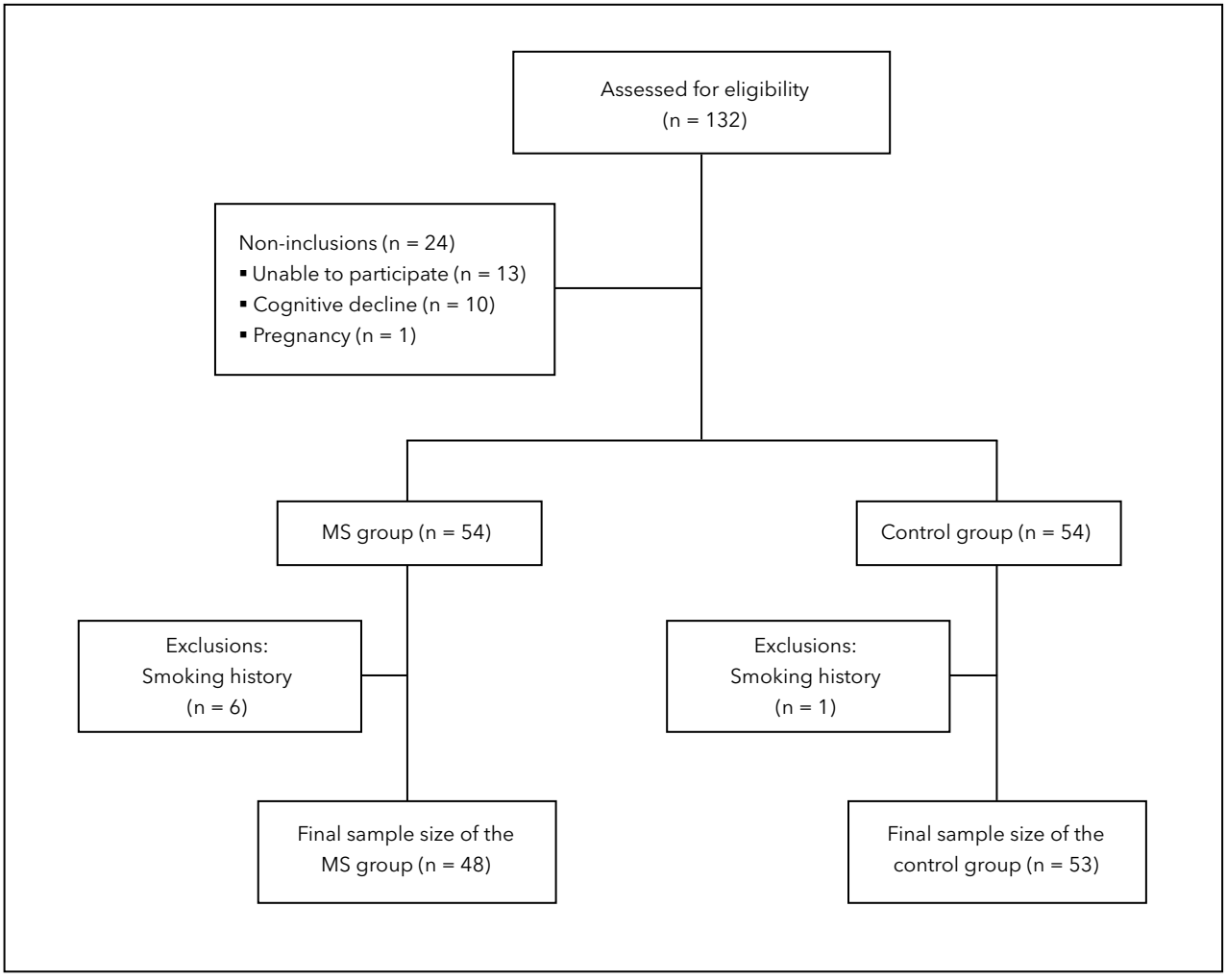

Figure 1 - Flow diagram of the study.

Note: MS = multiple sclerosis.

Prior the motor and respiratory assessments, participants were submitted to a sociodemographic questionnaire. In addition, the subjects had their cognition assessed with a general cognitive function test (Mini-Mental State Examination)[17] and with a specific instrument for executive processes (Montreal Cognitive Assessment).[18] These variables were included for characterization purposes. Disease severity of the MS group was evaluated with the Expanded Disability Status Scale.[19] Table 1 details the sociodemographic and clinical conditions of participants from MS and control groups.

Table 1 - Socio-demographic profile of participants of multiple sclerosis (MS) and control groups

Variables	MS group	Control group	p
Sample size (n)	48	53	0.619
Age (years)	37.4 ± 11.2	37.2 ± 10.4	0.922
Sex (female:male)	37:11	41:12	0.974
Occupation (%)			
Student	10.4	24.5	0.003
Retired	27.1	3.8	
Work	62.5	67.9	
Stay-at-home	0.0	3.8	
Education (%)			
Stay-at-home	0.0	3.8	0.142
Elementary education	4.1	5.7	
Secondary education	29.2	13.2	
Higher education	66.7	81.1	
Weight (kg)	68.5 ± 19.9	72.0 ± 14.8	0.322
Height (m)	1.6 ± 0.1	1.6 ± 0.1	0.972
Body mass index (kg/m^2)	25.1 ± 6.0	26.4 ± 5.1	0.256
Expanded Disability Status Scale (score)	3.1 ± 2.7	---	---
Mini-Mental State Examination (score)	28.2 ± 1.9	28.7 ± 1.9	0.184
Montreal Cognitive Assessment (score)	27.3 ± 5.4	27.5 ± 3.2	0.857

Note: Data are presented in number of events and percentage for categorical variables, and mean ± standard deviation for continuous variables; p-value of the chi-square test for the categorical variables and p-value of the Student's t-test for the continuous variables.

Motor functions

Motor functions were assessed with mobility, balance, and postural stability tests. The Timed Get Up and Go test (TUG)[20] was used to analyze participants' mobility. The test measures the time and number of steps needed for an individual to stand up from a chair, walk a distance of three meters, turn, walk back to the chair and sit down. Higher values indicate higher insecurity in the individual's performance.

The Berg Balance Scale (BBS)[21] assessed the balance of the participants. The instrument is composed of fourteen items involving specific tasks at different situations and support bases. Its scores varies between 0 and 56, with higher scores indicating a better balance of the subject.

Stabilometric analyses was assessed through the Biomec 400_V4 force platform (EMG System®, Brazil). Under a force platform composed of four load cells, participants performed all the tests barefoot and they were instructed to remain standing up for 60 seconds. Body position in space (cm), support base area (cm^2) and velocity of postural control (cm/s) were used to evaluate the balance of the subjects. Normative values on force platform were used according to parameters seen in the control group (matched in terms of sociodemographic parameters) and to the study of Scarmagnan et al.[22] (seeking to see the impact of age). Negative values on body position indicate changes in the center of mass toward back and left. Two researchers remained on each side of the participants during the assessments, in order to prevent falls.

Respiratory functions

Respiratory functions were analyzed with manovacuometry and spirometry tests. Manovacuometry was assessed with MVD300 manovacoumeter (Globalmed®, Brazil). The maximum inspiratory pressure was obtained starting at residual volume with the subject seated, wearing a nose clip and with a rigid, plastic, flanged mouthpiece. A small leak was introduced between the occlusion and the mouth to prevent glottic closure. The maneuver was undertaken five times, with a minimum of three correct measurements being accepted.[23]

Spirometry was carried out by using the Koko spirometer (nSpire Health Inc.®, USA) and following the American Thoracic Society recommendations.[24] Participants remained in seated, comfortable position, and were requested to "inflate" the lungs up to total lung capacity. Subsequently, subjects were requested to perform a maximum expiration in the device, showing at least three acceptable flow-volume curve tests for results reproduction. Predicted values were calculated according with normality references established by Pereira et al.[25] The assessed parameters were forced vital capacity, peak expiratory flow, and forced expiratory volume in the first second. Results were analyzed in raw values and they were categorized according participants' flow-volume curves in clinical reports (normal ventilation, obstructive, restrictive or mixed ventilatory disorders).

For the statistical procedure, the data were first processed using descriptive statistics (mean, standard deviation and number of events). Shapiro-Wilk test confirmed parametric pattern of the data. Comparisons between groups were performed with Student´s t-tests on continuous variables and chi-square tests on categorical variables. Pearson's correlation coefficients were applied to verify association between motor and respiratory functions in MS. Significance was set at 5%.

Results

One hundred one participants completed the trial. Patients with MS needed more time and steps to perform the Timed Get Up and Go test than subjects of the control group. In addition, scores of the BBS and stabilometric measures (support base area and imbalance speed) confirmed worse motor function of subjects with MS. Table 2 details mobility, balance and postural stability of participants from both groups.

Spirometric tests indicated normal parameters for pulmonary flows and lung capacities in both groups. Manovacuometric scores, differently, pointed to a respiratory muscle weakness in almost half of the participants of the MS group. Table 3 details respiratory functions of the MS and control groups.

Table 4 shows correlation analyses between motor and respiratory functions in MS. Respiratory functions were more associated with dynamic than static tasks. Negative values in correlation analyses indicate that lower scores in pulmonary parameters are related to a worse result on the Timed Get Up and Go test (increasing time and number of steps) and to a higher risk of imbalance (larger support base area). Positive correlations with the BBS shows that as lower the respiratory variable were, the lower was the score of the BBS.

Table 2 - Motor evaluation of the participants

Variables	Multiple sclerosis group	Control group	p
Timed Up and Go			
Time (sec)	9.9 ± 5.0	6.5 ± 1.2	0.001
Steps (n)	13.2 ± 3.8	10.2 ± 1.4	0.001
Berg Balance Scale (score)	49.1 ± 10.0	55.9 ± 0.1	0.001
Stabilometry			
Antero-posterior position (cm)	-1.6 ± 2.3	-1.8 ± 2.4	0.604
Mid-lateral position (cm)	-0.6 ± 1.4	-0.5 ± 0.6	0.815
Area (cm^2)	17.6 ± 14.2	6.5 ± 2.8	0.001
Antero-posterior speed (cm/s)	2.7 ± 2.0	1.6 ± 0.5	0.001
Mid-lateral speed (cm/s)	2.9 ± 1.8	1.7 ± 0.4	0.001

Note: Data are presented in mean ± standard deviation; p-value of Student´s t-test.

Table 3 - Respiratory functions in participants of multiple sclerosis and control groups

Variables	Multiple sclerosis group	Control group	p
Peak expiratory flow			
Liters/second	4.5 ± 2.3	5.0 ± 2.0	0.186
Percentage	56.5 ± 25.6	64.0 ± 24.4	0.134
Forced vital capacity			
Liters	3.3 ± 0.6	3.3 ± 0.7	0.726
Percentage	88.9 ± 11.3	89.7 ± 12.7	0.746
Ratio FEV in the first second and FVC (%)	83.7 ± 14.2	88.5 ± 8.9	0.040
Maximum inspiratory pressure (cm H_2O)	71.2 ± 29.3	88.1 ± 27.3	0.004
Maximum inspiratory pressure report (%)			
Normal parameters	52.1	77.4	0.008
Muscle weakness	47.9	22.6	

Note: FEV = forced expiratory volume; FVC = forced vital capacity. Data are presented in mean ± standard deviation and percentage; p-value of Student´s test for continuous variables and chi-square for categorical variables.

Table 4 - Correlation analyses between motor and respiratory functions in multiple sclerosis

Motor variables	Respiratory variables				
	PEF	FCV	FEV1	FEV1/CVF	MIP
Timed uUp and Go					
Time	-0.281*	-0.350*	-0.338*	-0.091	-0.241
Steps	-0.316*	-0.334*	-0.312*	-0.089	-0.390*
Berg Balance Scale (stabilometry)					
Antero-posterior position	0.086	0.179	0.035	-0.122	-0.002
Mid-lateral position	0.189	0.056	0.081	0.041	-0.054
Area	-0.235	-0.124	-0.341*	-0.357*	-0.432*
Antero-posterior position	0.021	-0.069	-0.098	-0.023	-0.172
Mid-lateral position	-0.067	-0.079	-0.151	-0.071	-0.171

Note: PEF = peak expiratory flow; FVC = forced vital capacity; FEV1 = forced expiratory volume in the first second; MIP = maximum inspiratory pressure. R values of the Pearson correlation index. *p < 0.05.

Discussion

This study investigated the impact of MS on subject's motor and respiratory functions. Results showed motor decline and respiratory muscle weakness in subjects with MS. Pulmonary flows and lung capacities presented normal parameters. Respiratory functions were more impacted by dynamic than static tasks. The understanding of these factors is important to analyze the impact of MS in subjects' everyday life.

The target of this study was people with MS. Seeking to control possible biases caused by discrepancies between the MS and control groups, subjects without MS were selected according to anthropometric and socio-demographic parameters of the MS group. Data presented in Table 1 indicate similarities between groups in all variables. Exception was for professional occupation, where there were more retired people in the MS than in the control group. Authors attribute this aspect to the impact of MS on patients' work environment.[26]

The clinical profile of people with MS was of patients in mild and moderate stages of the disease. This pattern is justified by the selection criteria, that required complex motor activities in which patients in severe stages may have difficulties in performing.[27] Authors encourage new studies addressing pulmonary and motor functions in people with greater physical impairment, an aspect not explored in this study. Motor functions were analyzed through static and dynamic tests. Authors included TUG test, BBS and a force platform assessment to provide a complete analysis of patients' functionality, so important in the practice of physical therapists.

Comparison between groups reinforces that motor impairment in MS occurs mainly in dynamic tasks.[28] In static activities, participants had similar values for body position and differences for support base area and speed of imbalance. Since physical therapists seek to promote patients' safety and independence, the results presented in motor tests should guide professionals before initiating exercise programs in subjects with MS.

Regarding the respiratory function, participants with MS had normal parameters of lung flow and pulmonary capacities, with similar results to the control group. This result corroborates Westerdahl et al.,[29] that found normal pulmonary function in MS with no significant abnormalities in dynamic spirometry tests.

Although some spirometric parameters presented differences in the comparison with healthy peers, this difference, though statistically significant, refers to normal values in both groups.[23-25]

The MS group had worse performance in the manuovacometry test in comparison to control peers. Almost half of patients with MS presented inspiratory muscle weakness. This finding is important and reinforces the need of therapies seeking to revert respiratory muscle weakness in people with MS, a field that still lacks scientific evidences.[30]

Some studies identified pulmonary problems in MS.[9-12] There is an important difference about the respiratory dysfunction common in later stages of MS than those presented in pulmonary diseases. In obstructive or restrictive pulmonary diseases such as COPD, asthma, cystic fibrosis, and interstitial lung disease, both respiratory muscle strength and lung volumes are affected.[31-33] Considering its pathophysiology, in pulmonary diseases there is a concomitant commitment of lung tissue and respiratory airways. In MS and other neurological conditions, differently, in the advanced stages it is common to have an indirect involvement of pulmonary structures and the commitment occurs mainly because of demyelination plaques in brain and brainstem.[34,35]

Age, physical immobility and performance fatigue are factors that can decrease motor function and respiratory muscle strength in MS.[11,36] In fact, results seen on force platform many times bring patients with MS closer to older adults rather than healthy control peers.[22]

In spite of not have been applied a specific questionnaire to measure fatigue in subjects with and without MS, Table 1 shows that subjects from both groups had similar age and none participant had immobility problems. Authors believe that those aspects were controlled in this study.

An interesting finding is that respiratory dysfunctions is more associated to dynamic motor tests than static stabilometric tests. The correlation indexes indicate that lower values in pulmonary parameters are related to a worse result on the TUG test and on the BBS. This may indicate a higher difficulty of subjects with MS in performing complex motor tasks that end up affecting other systems, like the respiratory. Authors encourage new studies aiming to confirm this premise.

The literature already confirmed the presence of cognitive decline in early and moderate stages of MS.[37,38] There is an important connection between cognition, respiratory and motor functions, which, if not controlled, could biased the results.[39,40] In this sense, we included two questionnaires to assess the cognitive functions of participants. Data indicated normal cognitive values in both groups, allowing the conclusion that such factor did not affect the results.

This study has two important limitations. First, the sample was formed by subjects in the mild and moderate stages of the disease. Further studies should be performed with patients in the advanced stage of MS. Second, this study concentrated analyses in inspiratory muscle strength. New studies should explore both inspiratory and expiratory muscle strength of subjects with MS.

Conclusion

Patients with MS present motor dysfunctions affecting mobility, balance and postural stability. Furthermore, subjects with MS showed an important commitment

of respiratory muscle strength. Associations between motor and respiratory variables indicate that respiratory functions are more impacted by dynamic than static tasks. The findings of this study should help physical therapists in the understanding of the clinical profile of patients with MS, which may guide new therapies seeking the improvement of patients' health status and quality of life.

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Authors´ contributions

All authors contributed equally in all stages of the study, except for patients' assessment, that was conducted by PDC, LLS, NMJ and JAD, and funding acquisition, that was obtained by GC.

References

1. Dobson R, Giovannoni G. Multiple sclerosis - a review. Eur J Neurol. 2019;26(1):27-40. DOI

2. Vidal-Jordana A, Montalban X. Multiple Sclerosis: Epidemiologic, clinical, and therapeutic aspects. Neuroimaging Clin N Am. 2017;27(2):195-204. DOI

3. Månsson E, Lexell J. Performance of activities of daily living in multiple sclerosis. Disabil Rehabil. 2004;26(10):576-85. DOI

4. Cameron MH, Nilsagard Y. Balance, gait, and falls in multiple sclerosis. Handb Clin Neurol. 2018;159:237-50. DOI

5. Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis. Gait Posture. 2017;51:25-35. DOI

6. Comber L, Sosnoff JJ, Galvin R, Coote S. Postural control deficits in people with multiple Sclerosis: A systematic review and meta-analysis. Gait Posture. 2018;61:445-52. DOI

7. Doty RL, MacGillivray MR, Talab H, Tourbier I, Reish M, Davis S, et al. Balance in multiple sclerosis: relationship to central brain regions. Exp Brain Res. 2018;236(10):2739-50. DOI

8. Stevens V, Goodman K, Rough K, Kraft GH. Gait impairment and optimizing mobility in multiple sclerosis. Phys Med Rehabil Clin N Am. 2013;24(4):573-92. DOI

9. Tzelepis GE, McCool FD. Respiratory dysfunction in multiple sclerosis. Respir Med. 2015;109(6):671-9. DOI

10. Farhat MR, Loring SH, Riskind P, Weinhouse G. Disturbance of respiratory muscle control in a patient with early-stage multiple sclerosis. Eur Respir J. 2013;41(6):1454-6. DOI

11. Ray AD, Mahoney MC, Fisher NM. Measures of respiratory function correlate with fatigue in ambulatory persons with multiple sclerosis. Disabil Rehabil. 2015;37(26):2407-12. DOI

12. Muhtaroglu M, Mut SE, Selcuk F, Malkoc M. Evaluation of respiratory functions and quality of life in multiple sclerosis patients. Acta Neurol Belg. 2020;120(5):1107-13. DOI

13. Mendes MA, Silva I, Ramires V, Reichert F, Martins R, Ferreira R, et al. Metabolic equivalent of task (METs) thresholds as an indicator of physical activity intensity. PLoS One. 2018; 13(7):e0200701. DOI

14. Snook EM, Motl RW. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. Neurorehabil Neural Repair. 2009;23(2):108-16. DOI

15. Gunn H, Markevics S, Haas B, Marsden J, Freeman J. Systematic review: The effectiveness of interventions to reduce falls and improve balance in adults with multiple sclerosis. Arch Phys Med Rehabil. 2015;96(10):1898-912. DOI

16. Gosselink R, Kovacs L, Ketelaer P, Carton H, Decramer M. Respiratory muscle weakness and respiratory muscle training in severely disabled multiple sclerosis patients. Arch Phys Med Rehabil. 2000;81(6):747-51. DOI

17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98. DOI

18. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9. DOI

19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52. DOI

20. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-8. DOI

21. Berg K, Wood-Dauphine S, Williams JI, Gayton D. Measuring balance in the elderly: preliminary development of an instrument. Physiother Can. 1989;41(6):304-11. DOI

22. Scarmagnan GS, Mello SCM, Lino TB, Barbieri FA, Christofoletti G. Negative effect of task complexity on the balance and mobility of healthy older adults. Rev Bras Geriatr Gerontol. 2021;24(1):e200120. DOI

23. Neder JA, Andreoni S, Castelo-Filho A, Nery LE. Reference values for lung function tests: I. Static volumes. Braz J Med Biol Res. 1999;32(6):703-17. DOI

24. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-88. DOI

25. Pereira CAC, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. DOI

26. Raggi A, Covelli V, Schiavolin S, Scaratti C, Leonardi M, Willems M. Work-related problems in multiple sclerosis: a literature review on its associates and determinants. Disabil Rehabil. 2016;38(10):936-44. DOI

27. Kalron A, Nitzani D, Achiron A. Static posturography across the EDSS scale in people with multiple sclerosis: a cross sectional study. BMC Neurol. 2016;16:70. DOI

28. Postigo-Alonso B, Galvao-Carmona A, Conde-Gavilán C, Jover A, Molina S, Peña-Toledo MA, et al. The effect of prioritization over cognitive-motor interference in people with relapsing-remitting multiple sclerosis and healthy controls. PLoS One. 2019;14(12):e0226775. DOI

29. Westerdahl E, Gunnarsson M, Wittrin A, Nilsagård Y. Pulmonary function and respiratory muscle strength in patients with multiple sclerosis. Mult Scler Int. 2021;2021:5532776. DOI

30. Rietberg MB, Veerbeek JM, Gosselink R, Kwakkel G, van Wegen EE. Respiratory muscle training for multiple sclerosis. Cochrane Database Syst Rev. 2017;12(12):CD009424. DOI

31. Yasuo M, Kitaguchi Y, Tokoro Y, Kosaka M, Wada Y, Kinjo T, et al. Differences between central airway obstruction and chronic obstructive pulmonary disease detected with the forced oscillation technique. Int J Chron Obstruct Pulmon Dis. 2020;15:1425-34. DOI

32. Karayama M, Inui N, Yasui H, Kono M, Hozumi H, Suzuki Y, et al. Physiological and morphological differences of airways between COPD and asthma-COPD overlap. Sci Rep. 2019;9(1):7818. DOI

33. Breuer O, Caudri D, Stick S, Turkovic L. Predicting disease progression in cystic fibrosis. Expert Rev Respir Med. 2018; 12(11):905-17. DOI

34. Taveira FM, Teixeira AL, Domingues RB. Early respiratory evaluation should be carried out systematically in patients with multiple sclerosis. Arq Neuropsiquiatr. 2013;71(3):142-5. DOI

35. Mutluay FK, Gürses HN, Saip S. Effects of multiple sclerosis on respiratory functions. Clin Rehabil. 2005;19(4):426-32. DOI

36. Bosnak-Guclu M, Gunduz AG, Nazliel B, Irkec C. Comparison of functional exercise capacity, pulmonary function and respiratory muscle strength in patients with multiple sclerosis with different disability levels and healthy controls. J Rehabil Med. 2012;44(1):80-6. DOI

37. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. Lancet Neurol. 2020;19(10):860-71. DOI

38. Sumowski JF, Benedict R, Enzinger C, Filippi M, Geurts JJ, Hamalainen P, et al. Cognition in multiple sclerosis: State of the field and priorities for the future. Neurology. 2018;90(6):278-88. DOI

39. Qiao H, Chen M, Li S, Li Y, Sun Y, Wu Y. Poor lung function accelerates cognitive decline in middle-aged and older adults: Evidence from the English Longitudinal Study of Ageing. Arch Gerontol Geriatr. 2020;90:104129. DOI

40. Al-Sharman A, Khalil H, El-Salem K, Alghwiri AA, Khazaaleh S, Khraim M. Motor performance improvement through virtual reality task is related to fatigue and cognition in people with multiple sclerosis. Physiother Res Int. 2019;24(4):e1782. DOI