Respiratory impairment in persons with multiple sclerosis: A cross-sectional study

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Abstract

Introduction: The spectrum of multiple sclerosis (MS) among all its clinical types includes a vast number of alterations. Of these, respiratory impairment carries big implications since this is an important cause of mortality and morbidity. **Methods:** Here, we present an observational study of respiratory assessment through spirometry in individuals with MS. Subjects who underwent autologous hematopoietic stem cell transplant from an interventional study were considered to participate. **Results:** An abnormal pattern of respiratory impairment was found in 147 participants; of this, 89.6% and 10.4% manifested a restrictive and obstructive pattern, respectively. The restrictive pattern was observed in 58 patients with secondary-progressive MS (SPMS) followed by 36 in patients with relapsing-remitting MS (RRMS) and, finally, 37 in patients with primary-progressive MS (PPMS). The full population had a mean forced expiratory volume of the 1st s (FEV1) of 92%, while the RRMS, PPMS, and SPMS groups had 93%, 89%, 91%, respectively. The median FEV1/forced vital capacity (FVC) ratio was 82.8% in the full cohort, 83.3% in the RRMS group, 83% in the PPMS group, and 82% in the SPMS group. Negative correlations were found between predicted FVC and FEV1 with expanded disability status scale and FEV1/FVC. **Conclusion:** This study showed a considerable number of restrictive patterns among all the participants, being the SPMS the type of MS with higher respiratory involvement and with functional disability.

Key words: Multiple sclerosis. Spirometry. Respiratory impairment.

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, and autoimmune disorder characterized by the destruction of the central nervous system (CNS) myelin with varying degrees of axonal damage that affects nerve conduction¹⁻⁴. This disease has a diverse and unpredictable course, leading to episodes of neurological

deficits followed by progressive neurological deterioration; its symptoms may include cognitive impairment, impairment of coordination, spasticity, muscle weakness, vision loss, and generalized fatigue. The clinical presentation of these symptoms may be relapsing, remitting, or progressive^{1,2}. MS usually affects young adults, being more frequent in women than in men with a ratio of 2:1^{1,4}.

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MS patients develop severe lung complications. Many may experience a reduced pulmonary respiratory inspiratory and expiratory muscle strength and/or diffusion capacity, leading to an impaired pulmonary function, even at the onset of MS. Such deterioration in pulmonary function may lead to ineffective cough, retention of secretions and inability to maintain clear airways, increasing the risk for the development of atelectasis and pneumonia.

Methods

Design

This is a cross-sectional observational study, derived from the population of the prospective, the interventional study “Outpatient Hematopoietic Grafting in MS Employing Autologous Peripheral Blood Stem Cells” (ClinicalTrials.gov identifier NCT02674217)⁴. The aim of the study was to assess and correlate the respiratory function and physical disability among individuals with MS who underwent hematopoietic stem cell transplantation (HSCT). As part of the HSCT protocol in our institution, all patients are assessed with pulmonary function tests (PFTs) as a baseline reference of the pulmonary function, since approximately 25% of the patients develop pulmonary complications within the 1st year of autologous HSCT⁵. Clínica Ruiz Institutional Review Board approved this study, and every participant signed and provided a consent document before the study.

Subjects

All patients who underwent treatment from July 2015 to November 2018 were included in the analysis. The inclusion criteria for the interventional study were as follows:

- Patients having relapsing-remitting, secondary progressive, and PPMS
- Karnofsky performance status of at least 70% and expanded disability status scale (EDSS) of 8 or below
- Not been treated with immune suppressant drugs 3 months before the study.

While the exclusion criteria were as follows:

- EDSS score higher than 8
- Karnofsky performance status lower than 70%
- Been exposed to chemotherapy in the past 3 months.

According to the relationship between fingolimod treatment and pulmonary dysfunction, we excluded all the subjects who had previous exposure to fingolimod⁶.

Groups were divided according to the clinical type of MS to analyze the differences in PFTs among the spectrum of the disease. Demographic and clinical variables (body mass index [BMI]), smoking status, age, etc.) were registered to compare them between the aforementioned groups.

Pulmonary function assessment

PFTs were carried out by trained physicians with Easy on-PC Spirometer (nidd Medizintechnik AG, Zürich, Switzerland). The spirometry was performed to all patients before the HSCT treatment, with the purpose of evaluating the pulmonary function before the administration of the different drugs required and also as a part of the pre-surgical evaluation before the Maharkar catheter placement. All subjects were recommended to avoid smoking, recent alcohol consumption, or consuming large meals before the test, according to international guidelines⁷⁻¹⁰. The volumes reported in this study included: forced vital capacity (FVC) and forced expiratory volume of the 1st s (FEV1) in liters (L) and predicted (%) values and FEV1/FVC ratio. The results of the pulmonary assessment were compared to reference values proposed by the NHANES III reference equations¹¹.

Statistical analysis

All statistical analyses were performed with Prism 7 (GraphPad Software, Inc. La Jolla, CA, USA) and Stata 14 (StataCorp LLC, College Station, TX, USA). For all the analyses, $p < 0.05$ was considered statistically significant. The data were assessed for normality with the D'Agostino and Pearson test. Data are expressed in mean and standard deviation for data with normal distribution, while median and interquartile ranges (IQR) were used for data without normal distribution. Pearson correlation coefficients were calculated to assess the association between the PFT parameters and EDSS values. Multiple linear regression was performed to adjust EDSS and respiratory parameters to confounding variables such as age, BMI, smoking status, and length of disease.

Results

Subjects

A total of 549 patients with MS were identified, from which, 83 were excluded since they had previous

Table 1. Demographic data

Variables	Global (n = 466)	RRMS (n = 196)	PPMS (n = 103)	SPMS (n = 167)	p
Male, female	170/296	51/145	58/45	59/108	< 0.0001
Age, mean	47.6 (SD 9.3)	44.7 (8.8)	49.2 (10.8)	50 (8)	< 0.0001
Baseline EDSS, median	6 (IQR 2.5)	4 (3.5)	6 (2)	6 (1)	< 0.0001
BMI, kg/m ²	25.4 (SD 5.3)	25.4 (5.2)	25.1 (5.3)	25.8 (5.3)	0.6
Ever smokers	162/466	67/196	49/103	44/167	0.02
Length of disease	11.3 (SD 8.3)	9.7 (8.2)	8 (6)	15 (8.4)	< 0.0001
Previous DMT	342/466	155/196	53/103	136/167	< 0.0001

BMI: body mass index; EDSS: expanded disability status scale; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Table 2. Pulmonary function assessment results

Variables	Total	PPMS	SPMS	RRMS	p
Spirometric pattern					0.002
Normal	319/466	62/319	109/319	148/319	
Obstructive	16/466	5/16	0/16	11/16	
Restrictive	131/466	36/131	58/131	37/131	
FVC					
FVC, mean (%)	88 (SD 17.56)	86 (SD 16.77)	86 (SD 15.24)	91 (SD 17.54)	< 0.0001
FVC, mean (L)	3.5 (SD 1.02)	3.46 (SD 1)	3.4 (SD 0.96)	3.65 (SD 1.04)	0.53
FEV1					
FEV1, mean (%)	92 (SD 17.57)	89(SD 17.15)	91(SD 15.99)	93 (SD 17.83)	0.95
FEV1, mean (L)	2.94(SD 4.8)	2.83 (SD 0.83)	2.7 (SD 0.77)	3.02 (SD 7.40)	0.3
FEV1/FVC					
FEV1/FVC, mean (%)	82.8 (SD 7.68)	83 (SD 7.20)	82 (SD 5.69)	83.3 (SD 8.09)	0.92
FEV1/FVC, mean (predicted)	104 (SD 9.77)	106 (SD 9.63)	104 (SD 7.35)	103 (SD 10.19)	0.0016

FEV1: forced expiratory volume of the 1st s; FVC: forced vital capacity; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

exposure to fingolimod. The study included 466 patients with relapsing-remitting MS (RRMS) (n = 196), primary-progressive MS (PPMS) (n = 103), and secondary-progressive MS (SPMS) (n = 167). The median age of the full cohort was 47 (IQR 42 - 65) being similar among the rest of the groups (Table 1); 296 of individuals were females and 170 males. In the PPMS, the proportion of females and males was almost 1:1, while in the RRMS and SPMS groups, this relation was 2:1 and 3:1, respectively. The registered BMI was similar among all groups: 24.1 RRMS, 24.5 PPMS, and 24.2 SPMS (Table 1). Registered smoking status consisted of 162 ever smokers of all 466 individuals (34%). The proportion of ever smokers among our population was 162/466, being the PPMS group the one with the highest proportion (50/103).

Pulmonary function assessment

Of the 466 assessed individuals, 147 (31.7%) patients were found to have an abnormal pattern of lung function. Of these patients, 131 (89.2%) and 16 (10.8%) patients had restrictive and obstructive patterns, respectively (Table 2). The median of predicted FVC was 88% for the full population, 91% in the RRMS group, 86% in the PPMS group, and 86.5% in the SPMS. The full population had a median FEV1 of 92%, while the RRMS, PPMS, and SPMS groups had 93%, 89%, and 91%, respectively. The median FEV1/FVC ratio was 82.8% in the full cohort, 83.3% in the RRMS group, 83% in the PPMS group, and 82% in the SPMS group (Table 2).

As for the spirometric patterns, 319 (68.3%) patients presented a normal result, 16 (3.3%) an obstructive

Table 3. Correlation between PFT parameters and clinical disability

Variables	Global	p	RRMS	p	PPMS	p	SPMS	p
FVC (%) - EDSS	-0.39	< 0.0001	-0.40	< 0.0001	-0.31	0.0008	-0.35	< 0.0001
FEV1 (%) - EDSS	-0.32	< 0.0001	-0.27	< 0.0001	-0.28	0.0030	-0.31	< 0.0001
FEV1/FVC - EDSS	0.12	0.038	0.13	0.56	0.07	0.45	0.12	0.08

EDSS: expanded disability status scale; FEV1: forced expiratory volume of the 1st s; FVC: forced vital capacity; PPMS: primary progressive multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation; SPMS: secondary progressive multiple sclerosis.

pattern, and 131 (28.4%) a restrictive pattern. From the patients who presented a restrictive pattern, 36 (27.4%) had PPMS, 58 (44.2%) SPMS, and 37 (28.4%) RRMS.

Correlation of PFTs parameters with clinical disability

To analyze and find a relation between pulmonary function and the disability caused by MS, Pearson coefficient was calculated, using the EDSS score as the standard parameter for disability measurement and the predicted values of FVC, FEV1, and FEV1/FVC ratio for pulmonary function and severity of restriction. The results showed a weak to moderate inverse correlation between predicted FVC and EDSS score, for the global ($r = -0.39$, $p \leq 0.0001$, 95% confidence interval [CI] $-0.46 - -0.32$), RRMS ($r = -0.40$, $p = 0.0001$, 95% CI $-0.51 - -0.28$), PPMS ($r = -0.31$, $p = 0.0008$, 95% CI $-0.48 - -0.13$), and SPMS ($r = -0.35$, $p \leq 0.0001$, 95% CI $-0.46 - -0.22$) (Table 3). The analysis showed weak to moderate negative correlations between predicted FEV1 and EDSS in the global ($r = -0.32$, $p \leq 0.0001$, 95% CI $-0.40 - -0.24$), RRMS ($r = 0.27$, $p \leq 0.0001$, 95% CI $-0.39 - 0.14$), PPMS ($r = 0.28$, $p \leq 0.003$, 95% CI $-0.44 - 0.09$), and SPMS ($r = -0.31$, $p \leq 0.0001$, 95% CI $-0.44 - 0.18$). The FEV1/FVC ratio and the EDSS score showed a weak positive correlation among all the groups (Table 3). The adjustment of FVC and FEV1 for EDSS, age, length of disease, BMI, and smoking status showed that, except for EDSS, these variables did not predicted FVC ($F[4, 461] = 19.68$, $p \leq 0.0001$, $R^2 = 0.14$) nor FEV1 ($F[4, 461] = 12.23$, $p \leq 0.0001$, $R^2 = 0.09$).

Discussion

Factors contributing to respiratory dysfunction in MS include weakness of the respiratory muscles, bulbar dysfunction, abnormal ventilatory control, and sleep-disordered breathing. Respiratory dysfunction contributes significantly to mortality and morbidity in MS¹².

Respiratory complications are one of the most common causes of death in MS¹²⁻¹⁶. In one large study, respiratory complications accounted for approximately 47% of all deaths in MS patients¹⁷. Recognizing which patients with MS are at increased risk for respiratory complications is critical as it may help the clinician to carefully evaluate these patients and initiate appropriate preventive measures. The pathophysiological hallmark of respiratory dysfunction in MS is the presence of demyelinating lesions in the CNS. These lesions may involve one or more locations associated with propagation of neural impulses to the respiratory muscles. Depending on the location and extent of demyelinating lesions, respiratory dysfunction may manifest with symptoms due to respiratory muscle weakness and impaired cough, dysfunction of bulbar muscles, abnormalities in the control of breathing, or respiratory failure. Additional factors such as drugs, disease-related fatigue, or nerve conduction block due to elevated body temperature may independently compromise respiratory muscle function.

Respiratory failure presents in the terminal stages of MS and is usually associated with significant bulbar or limb paralysis¹⁸. It is uncommon in ambulatory patients. Respiratory failure may be acute, typically secondary to demyelinating lesions in the cervical cord or the medulla, or chronic, typically found in the terminal stages of the disease and related to weak respiratory muscles, and ineffective cough, leading to aspiration, atelectasis, and pneumonia¹⁸⁻²⁰. Of the two types, only acute respiratory failure is potentially reversible with treatment¹⁹.

Acute respiratory failure is a rather uncommon entity. Its clinical characteristics primarily have been described in single cases or small patient series^{18,19,21-27}. Patients at risk are those with the relapsing-remitting form of MS and new extensive demyelinating plaques¹⁹, with acute respiratory failure occurring after a median of 6 years from disease onset. Dyspnea, orthopnea, or confusion often develops over hours or days in patients with no preexisting respiratory dysfunction. Rapid shallow breathing with diminished abdominal excursions or abdominal paradox

Table 4. Pulmonary function assessment in different international cohorts

Reference	n	Age (SD)	EDSS (range)	FVC (%)	FEV1 (%)	FEV1/FVC (%)
Levy et al. ¹⁰	73	55 (SD 8.7)	Median 8 (mean 8.09 SD 0.67)	-	53.6 (SD 28.7)	-
Ray et al. ¹¹	37	52.7 (SD 10.2)	3.5 (SD 1.9) 1-6.5	3.7 (SD 0.8) 105.2 (SD 18)	2.9 (SD 0.6) 108.3 (SD 20.1)	0.80 (SD 0.1)
Westerdahl et al. ¹²	25 (control group)	56 (SD 9)	4.5 (1.5-8)	3.7 (SD 1.1)	2.8 (SD 0.7)	74.8 (SD 6.6)
	23 (interventional group)	55 (SD 12)	5.0 (3.0-7.0)	3.3 (SD 0.8)	2.6 (SD 0.7)	78.4 (SD 7.1)
Ray et al. ¹³	10 (control group)	56.2 (SD 8.8)	4.4 (SD 2.1) 1.0-6.0)	3.62 (SD 1.05) 103.0 (SD 22.0)	3.07 (SD 0.95) 109.0 (SD 25.0)	-
	11 (interventional group)	50.9 (SD 5.7)	3.2 (SD 1.9) 1.0-6.5	3.39 (SD 0.67) 98.0 (SD 18.0)	2.75 (SD 0.52) 99.0 (SD 17.0)	-
Bosnak-Guclu, et al. ¹⁴	23 (no-minimal disability)	33.3 (SD 6.31)	1.0 (1.0-2.0)	105.39 (SD 12.16)	98.22 (SD 14.59)	82.14 (SD 8.81)
	20 (mild-relatively severe disability)	38.15 (SD 8.31)	3.5 (2.5-4.5)	101.95 (SD 14.17)	97.15 (SD 11.18)	83.51 (SD 6.37)
Present study	466	47 (SD 9.23)	6 (SD 1.81)	88 (SD 17.56)	92 (SD 17.57)	82.8 (SD 7.68)

EDSS: expanded disability status scale; FEV1: forced expiratory volume of the 1st s; FVC: forced vital capacity; SD: standard deviation.

occurs when there is marked diaphragmatic weakness¹⁹. FVC is markedly diminished, with values often being < 1 L. A decrement of vital capacity (VC) in the supine position of more than 30% of that measured in the upright position is indicative of bilateral diaphragm dysfunction²⁸ and may be seen in a significant proportion of patients with acute respiratory failure¹⁹. On magnetic resonance imaging (MRI), individuals often have demyelinating lesions involving the medulla or the spinal cord interfering with motor output to the respiratory muscles. In the series of Howard et al., the majority of patients had quadriplegia, or spastic paraplegia with upper arm weakness, of moderate or severe degree¹⁹.

The chronic type of respiratory failure usually occurs in the terminal stages of the disease and is associated with significant bulbar dysfunction¹⁹. Typically, these patients are wheelchair-bound, with upper extremity weakness and weak respiratory muscles¹⁹. Frequent episodes of aspiration and atelectasis in conjunction with respiratory muscle weakness and a weak cough may lead to bouts of pneumonia and frequent hospitalizations. However, advanced respiratory support with mechanical ventilation and/or permanent tracheostomy is unusual in Pittock et al. described 22 MS patients over 33 years who required mechanical ventilation or tracheostomy²⁵. The most common indications for mechanical

ventilation or tracheostomy were aspiration pneumonia and mucous plugging and difficulty in removing bronchial secretions²⁵. The majority of patients had progressive MS, with a median survival of 22 months following mechanical ventilation²⁵.

PFT may provide clues as to whether respiratory muscle dysfunction is present. Lung volumes, such as total lung capacity, VC, and residual volume, may be reduced in patients with severe respiratory muscle weakness. However, the strength of the respiratory muscles must be reduced to as much as 50% of predicted before any significant reduction in lung volume is measured¹. Thus, these lung volumes may be normal in patients with mild to moderate respiratory muscle weakness^{20,28,29} and are likely diminished in bedridden patients who have respiratory muscle weakness³⁰. FVC is usually within the normal range in ambulatory or ambulatory with assistance (EDSS < 7) MS patients.

In contrast, FVC is moderately decreased in wheelchair-bound and severely decreased in bedridden patients^{20,31-35}. Similar changes were also reported for FEV1 and maximal voluntary ventilation (MVV). Besides, FVC does not correlate with the duration of disease^{31,34}. In several studies^{20,30-34,36}, the FVC and/or MVV correlated with the level of disability as assessed by the EDSS scale.

Our study found correlations between predicted FVC and FEV1 and EDSS scores among all the groups, similarly to the reports from Pinedo et al., Pittcock et al., and Katsenos et al.^{24,25,27} These findings may represent a progressive respiratory dysfunction, even in the RRMS group. However, longitudinal studies about these phenomena may be needed. In comparison with other series from cross-sectional studies and randomized clinical trials (Table 4) our population consisted of older and more affected individuals. However, spirometry parameters remain somewhat similar, which may represent a more advanced stage of respiratory dysfunction but with the same pattern of evolution.

Several studies have been done with the aim of analyzing the relation between spirometric parameters and the severity of MS; nevertheless, these studies used a low sample to find this correlation. In 2017, Levy et al. analyzed 73 patients with severe MS, finding a relation between the severity of the disease and a restrictive pattern on spirometry³⁷. In contrast with other studies, our group of 514 patients supports this study as one with the largest population. The patients analyzed in this work included patients with three different types of MS (RRMS, PPMS, and SPMS), giving the study a more significant outlook of how the disease is behaving in the pulmonary function in each type of MS.

Although our study showed congruent and compatible results with previous studies, these have to be interpreted with caution, since simple spirometry was performed as a means to evaluate the respiratory function in this population. As previously used by Ray et al. and Bosnak-Guclu et al., there is a vast number of tests available to assess the complex respiratory changes observed in individuals with MS, which may help to establish a further characterization of respiratory dysfunction in these patients³⁸⁻⁴¹. Another limitation accounts for the fact that only EDSS was employed as a measure of clinical and physical disability. The inclusion of additional objective measures, such as MRI outcomes, could provide more in-depth information about the relationship between the respiratory function and the load of brain and spinal cord damage.

Conclusion

Respiratory dysfunction in individuals with MS has a rather specific pattern of presentation consisting of restriction. This study showed a considerable number of restrictive patterns among all the participants, being the SPMS the type of MS with higher respiratory involvement. The parameters used in simple spirometry had

a moderate correlation with the level of disability among all the groups; this could be further analyzed to establish the role of PFTs in the comprehensive evaluation of MS.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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