Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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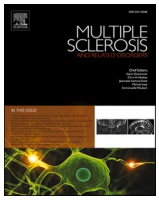

Original article

Fear of COVID-19, problems accessing medical appointments, and subjective experience of disease progression, predict anxiety and depression reactions in patients with Multiple Sclerosis

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ABSTRACT

Background: During the current COVID-19 pandemic there are studies that have suggested a negative impact of the pandemic on the mental health of patients with multiple sclerosis (PwMS). In this sense, several factors may be related to the increase in experiences of anxiety and depression in PwMS during the current pandemic.
Objective: In this study we first explored the reactions of anxiety, depression and fear to COVID-19 in a group of PwMS that belong to the Ibero-American region. Besides, we explored whether having been positive to COVID-19, fear of COVID-19, the obstacles to attend medical appointments during the outbreak and subjective experience of MS progression, could predict the anxiety and depression reactions in our PwMS sample.
Materials and methods: An online cross-sectional survey was conducted on 202 MS patients from six countries (Argentina, Mexico, Spain, Dominican Republic, Venezuela and Cuba). For comparisons between variables an independent-samples t-test and one-way analysis of variance were used. Multiple linear regression was used to evaluate the effects of potential predictor variables over emotional reactions.
Results: Our results showed that PwMS who were positive for COVID-19 reported higher levels of fear of COVID-19 ($p<.001$) and also higher levels of anxiety ($p<.001$) compared to non-positive patients. Those patients who had difficulties attending their medical appointments during the outbreak showed higher levels of depression ($p=.03$) and anxiety ($p=.019$). Levels of anxiety ($p<.001$) and depression ($p=.006$) were also higher among patients with the subjective experience of MS disease progression. The reactions of fear of COVID-19, having been positive to COVID-19, problems attending medical appointments, and subjective experience of MS disease progression showed a high association with the negative impact of the pandemic on mental health of PwMS.
Conclusions: Our results show that the situation generated by the COVID-19 pandemic has had a negative impact on the mental health of PwMS in our sample. Our results also alert to the importance of offering psychological care to patients with multiple sclerosis during the current outbreak, regardless of whether they have been positive for COVID-19.

1. Introduction

The COVD-19 pandemic and the social measures to control it, have posed a challenge to the mental health of the general population around the world (Pfefferbaum and North, 2020). Up to now studies conducted in the general population, an increase in reactions of fear, anxiety, depression, post-traumatic stress symptoms has been reported. (PTSS) (Brooks et al., 2020; Galea et al., 2020; Qiu et al., 2020; Rossi et al., 2021; Torales et al., 2020; Vindegaard and Benros, 2020; Wang et al., 2020; Xiang et al., 2020).

In patients 60+ years and infected with SARS-CoV-2, the presence of non-communicable chronic diseases (hypertension, diabetes, obesity,

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etc.), respiratory comorbidities, and neurological impairments, are among the factors that have been associated with a worse outcome (Grasselli et al., 2020; Herman et al., 2020; Li et al., 2020; Serrano-Catro et al., 2020).

In Multiple Sclerosis (MS), there are studies suggesting a negative impact of this pandemic on the mental health of patients with MS (PwMS). For example, a study done in Italy explored how the lockdown period impacted on the mental health of patients in comparison with healthy controls (Motolese et al., 2020). The authors reported that, MS patients, compared with the general population, presented a higher burden of depressive symptoms, a worse sleep quality and perceived an increase in fatigue level.

Additionally, during the current outbreak, higher levels of anxiety, depression and stress have been observed in PwMS when compared to their caregivers (Talaat et al., 2020). Another study was also carried out in the United States, during the first wave of the pandemic; it reported that the PwMS, included in the sample, experienced clinically significant levels of depression and/or anxiety related to COVID-19 pandemic (Alschuler et al., 2021).

A recent study conducted in Iran, explored the prevalence of anxiety, depression, and levels of fear of COVID-19, in PwMS during COVID-19 pandemic (Ramezani et al., 2021). The authors reported that, during the COVID-19 pandemic, the prevalence of anxiety and depression was 31.2% and 39.3% respectively in the PwMS sample. In these patients, levels of anxiety and depression showed a high association with levels of fear of COVID-19.

Several factors may be related to the increase in experiences of anxiety and depression in PwMS during the current pandemic. Some of these factors could be related to stressors directly related to the pandemic, such as social distancing, isolation, quarantines, economic uncertainty, the uncertainty of contracting a highly contagious disease (or the possibilities their relatives close to them could get sick) (Chiaravalloti et al., 2020; Ramezani et al., 2021). PwMS experience additional stressors. For example, in some cases there are patients who receive disease-modifying therapies (DMTs). This DMTs cause significant immune suppression (Giovannoni et al., 2020), which can increase the fear of getting sick. In addition, measures of physical distancing can be an obstacle for patients to attend cognitive and physical rehabilitation (Motolese et al., 2020) and if patients do not attend these services the levels of psychological distress may increase.

During the current pandemic, other potentially stressors and their relationship to the psychological response of PwMS are still unknown. For example, it is important to delve into the impact of the COVID-19 diagnosis on the mental health of these patients. In addition, quarantine measures can limit the access to medications, and keep patients from attending follow-up consultations; thus, uncertainty about the possibility of disease progression can increase.

In this study we first explored the reactions of anxiety, depression and fear to COVID-19 in a group of patients with multiple sclerosis that belong to the Ibero-American region. A comparison between the psychological reactions scores during the COVID-19 pandemic was made in relation to sociodemographic variables such as age, gender and country.

Besides, we explored whether having been positive to COVID-19, fear of COVID-19, the obstacles to attend medical appointments during the outbreak and subjective experience of MS progression, could predict the anxiety and depression reactions in our PwMS sample. Our results will allow the design of interventions to reduce the negative psychological impact of the current pandemic on patients with multiple sclerosis.

2.1. Methods

2.2. Study design and participants

A cross-sectional online study was designed. Potential patients were invited to participate in the study through phone calls and WhatsApp and Facebook groups. In the case of telephone calls, the telephone numbers were extracted from the medical records of the patients by their neurologist. In addition, administrators of WhatsApp and Facebook groups specifically dedicated to PwMS were contacted. The authors explained the objectives of the study to the group administrators and subsequently shared the questionnaire link. To disseminate the survey, the Google Forms® platform was used. The research was conducted between January 23 and February 15, 2021.

A total of 212 PwMS completed the questionnaire. Of the total sample, 2 participants were excluded because they were less than 18 years old. Additionally, 8 patients were also excluded for having a relapse of the disease during the last 1 months or for being going through one. The final sample was made up of 202 MS patients from six countries (Argentina, Mexico, Spain, Dominican Republic, Venezuela and Cuba).

2.3. Measures

Demographic and Clinical Information: The demographic variables included the patient age, education level, marital status and country. The clinical variables included if the patient was positive to COVID-19, MS phenotype and MS disease duration. Additionally, *ad hoc* questions were developed to explore whether the patient had presented difficulties in getting their medications during the pandemic (“did you have trouble getting your medications during the outbreak?”), Attend consultations (“did you have problems attending your medical appointments during the outbreak? ”) and if they considered that the disease had progressed during the last year (“ comparing with your state of health before the outbreak, do you feel that your disease has progressed? ”).

For questions related to access to medicines and medical consultations, the response options were (1) never; (2) sometimes; (3) frequently and (4) very frequently. In the case of self-perceived health related to the progress of the disease, the response options were (1) I feel the same as before, (2) I feel different but not too much, (3) I feel that the disease has progressed and (4) my illness has progressed a lot. For the purposes of data analysis, options 1 and 2 were classified together as “no” while options 3 and 4 were grouped together under the label “yes”.

Fear of COVID-19 Scale (FCV-19S) (Ahorsu et al., 2020): The FCV-19S is made up of 7 items with a five-item Likert-point response from 1 (“strongly disagree”) to 5 (“strongly agree”). The score range of the FCV-19S is 7 to 35. Higher scores indicate greater fear of COVID-19.

Beck Depression Inventory-II (BDI-II) (Beck et al., 1996): The BDI-II is a 21-item, multiple-choice scale that explores the presence and severity of depression symptoms. Each item has four response options. The total score is obtained from the sum of the options selected by the participant. A higher score indicates greater depression. In the case of the evaluation of depression in multiple sclerosis, the BDI-III has shown adequate psychometric properties (Watson et al., 2014).

Generalized Anxiety Disorder Scale (GAD-7) (Spitzer et al., 2006): The GAD-7 is a widely used self-report scale developed to screen for GAD. Each item is scored on a four-point Likert scale (0–3) with total scores ranging from 0 to 21. A higher score indicates greater anxiety severity. GAD-7 has shown adequate psychometric properties in the evaluation of GAD in multiple sclerosis (Terrill et al., 2015).

2.4. Procedure

The study protocol was approved by the ethics committee of the Department of Psychology of the Universidad Central "Marta Abreu" de Las Villas. All procedures performed in this study were in accordance with the ethical standards of the 1964 Helsinki Declaration. Informed consent was obtained from all participants included in the study.

2.5. Data analysis

The data were processed using SPSS/Windows (version 21). Descriptive statistics was used to explore participants’ characteristics.

Depression, anxiety and fear reactions were compared between different demographic and clinical variables. For comparisons between dichotomous variables an independent-samples t-test was conducted. Comparisons between more than two groups were conducted using one-way analysis of variance and post-hoc comparisons using Tukey HSD test. Results with $p < 0.05$ were regarded as significant. Multiple linear regression was used to evaluate the effects of COVID-19 positivity, problems attending medical appointments during the outbreak and subjective experience of MS progression during the pandemic over emotional variables (depression and anxiety).

3. Results

3.1. Characteristics of the sample

Demographic information for 202 PwMS is summarized in Table 1. The mean age of participants ($n = 202$) was 42.76 years with a range between 18 and 75 years old, and female gender predominated in the sample (72.6%). In our sample most of the participants had a university-level degree (52%). Additionally, the 51% of the patients were married.

Clinical information for patients is summarized in Table 2. In our sample, 41(20.3%) of patients were positive to COVID-19 disease. Of the 202 MS patients 69.3.5% ($n = 140$) had relapsing remitting MS (RRMS) and the mean duration since disease onset was 9.56 ± 8.5 years. Most of the participants did not had difficulties getting their medications (74.3%) or attending medical appointments related to MS (68.8%) during the outbreak. On the other hand, most patients (70.8%) had the subjective experience that their disease had progressed during the pandemic. All subgroups of MS phenotypes present in the study reported the subjective experience of disease progression (RRMS (74.1%), PPMS (7.7%), SPMS (4.9%), PRMS (3.5%) and also those who did not know their phenotype (9.8%)).

3.2. Between-group differences

Table 3 gives an overview of the differences between sociodemographic variables and psychological reactions. In our sample we did not find differences in the reactions of fear, depression and anxiety between age groups, genders or country of origin. On the other hand, and as expected, PwMS who were positive for COVID-19 reported higher levels of fear of COVID-19 and also higher levels of anxiety (Table 4). However, depression did not show differences between COVID-19 positive patients and uninfected patients. Additionally, those patients who had difficulties attending their medical appointments during the outbreak showed higher levels of depression and anxiety, compared to those who did not have problems to visit their neurologist.

Levels of anxiety and depression were also higher among patients who manifested the subjective experience of MS disease progression. Finally, the experiences of fear, depression and anxiety did not show differences in relation to access to medications for the management of multiple sclerosis.

Table 1
Participant demographic data.

Demographic variable	Mean ±SD or n(%)
Age	42,76±12,69
Age (range)	
18-30	40(19,8)
31-40	56(27,7)
41-50	47(23,3)
51+	59(29,2)
Gender	
Female	154(76,2)
Male	48(23,8)
Education	
Primary education	6(3)
Middle School	29(14,4)
High School	39(19,3)
University Degree	105(52)
Postgraduate Education	23(11,4)
Marital status	
Single	73(36,1)
Married/Domestic partner	103(51)
Divorced	26(12,9)
Country	
Argentina	39(19,3)
Mexico	38(18,8)
Spain	32(15,8)
Dominican Republic	32(15,8)
Venezuela	31(15,3)
Cuba	30(14,9)

Note.SE(Standard Deviation)

Table 2
Participant clinical data.

Clinical variable	Mean±SD or n (%)
Positive to COVID-19	
Yes	41(20,3)
No	161(79,7)
MS Phenotype	
Relapsing-Remitting (RRMS)	140(69,3)
Primary-Progressive (PPMS)	20(9,9)
Secondary-Progressive (SPMS)	13(6,4)
Progressive-Relapsing (PRMS)	8(4)
I Dont Know	21(10,4)
Disease duration years	9,56±8,5
Did you have trouble getting your medications during the outbreak?	
Yes	52(25,7)
No	150(74,3)
Did you have problems attending your medical consultations during the outbreak?	
Yes	63(31,2)
No	139(68,8)
Comparing with your state of health before the outbreak, do you feel that your disease has progressed?	
Yes	59(29,2)
No	143(70,8)
BDI total score	16,18±12
GAD-7 total score	8,91±5,44
FCV-19S total score	21.54±5,84

Note.SE(Standard Deviation)

3.3. Regression analysis

A multiple regression analysis was run to explore the association of COVID-19 positivity, fear of COVID-19, problems attending medical appointments during the outbreak and subjective experience of MS progression during the pandemic with emotional variables (depression and anxiety) (Table 5).

The overall model for depression was significant ($F(4,201) = 10.32$, $p < 0.001$), accounting for 27.2% of the variance in depression scores. Fear of Covid-19 and problems attending medical appointments showed a significant association with higher levels of depression, explaining 17.1% and 11.8% of the variance in depression reactions. Additionally, the subjective experience of MS disease progression during the pandemic was significantly associated with higher depression levels accounting for 32% of the variance in depression experience.

On the other hand, the overall model for anxiety was also significant ($F(4,201) = 36.18$, $p < 0.001$), accounting for 41.2% of the variance in fear scores. In the sample having had positive to COVID-19 and fear of COVID-19 were significantly associated with higher anxiety, accounting for 55.9% and 13.2% of the variance in anxiety experience. Additionally, the subjective experience of MS disease progression during the pandemic was also significantly associated with higher anxiety levels accounting for 19.1% of the variance.

Table 3
Comparisons between sociodemographic variables and psychological reactions

Psychological reaction						
	Fear of COVID-19		Anxiety		Depression	
Variable	Mean±SD	p value	Mean±SD	p value	Mean±SD	p value
Age						
18-30	22.33±5.31	F(3.20)=.644, p=.58	9.90±5.51	F(3.20)=2.38, p=.07	16.75±9.93	F(3.20)=.824, p=.48
31-40	22.0±6.19		9.82±5.78		17.80±14.25	
41-50	20.70±5.32		8.79±4.90		16.06±10.97	
51+	21.32±6.27		7.47±5.28		14.36±11.82	
Gender						
Female	21.77±5.99	t(200)=.965, p=.33	9.22±5.54	t(200)=1.45, p=.14	16.38±11.64	t(200)=.409, p=.68
Male	20.83±5.34		9.92±5.04		15.56±13.21	
Country						
Argentina	19.64±5.21	F(5.20)=1.97, p=.08				
	9.08±5.36	F(5.20)=.70, p=.60				
	16.82±10.75	F(5.20)=1.29, p=.26				
Mexico	21.47±6.9		8.39±5.92		16.97±14.80	
Spain	21.88±4.50		10.28±5.76		21.06±14.14	
DR	21.66±6.52		9.22±5.30		12.75±9.91	
Venezuela	22.19±6.12		7.94±5.12		13.71±9.84	
Cuba	22.97±5.02		8.57±5.15		15.37±10.05	

Note.SE(Standard Deviation)

Table 4
Comparisons between variables related to Covid-19 and psychological reactions

Psychological reaction						
	Fear of COVID-19		Depression		Anxiety	
Variable	Mean±SD	p value	Mean±SD	p value	Mean±SD	p value
Positive to COVID-19						
Yes n=41	26.09±3.48	t(200)=3.716,p<.001	15.93±12.16	t(200)=.153,p=.87	16.92±5.18	t(200)=10.22, <.001
No n=161	24.00±4.63		16.25±12.0		8.47±1.99	
Did you have trouble getting your medications during the outbreak?						
Yes n=52	24.43±4.31	t(200) =.014,p=.98	17.17±12.47	t(200)=.689,p=.49	9.58±4.91	t(200) =1.024, p=.30
No n=150	24.42±5.02		15.84±11.86		8.68±5.61	
Did you have problems attending your medical appointments during the outbreak?						
Yes n=63	24.29±4.49	t(200) =.636,p=.52	18.70±13.41	t(200)=2.02,p=.03	11.61±5.74	t(200) =2.37, p=.019
No n=139	24.73±4.52		14.04±11.18		9.54±5.74	
Do you think your disease has progressed during the pandemic?						
Yes n=143	24.30±4.39	t(200) =.986,p=.32	17.90±10.25	t(200)=3.34,p=.001	11.48±5.36	t(200) =2.76, p=.006
No n=59	23.50±5.04		11.84±10.36		8.73±5.81	

Note.SE(Standard Deviation)

Table 5
Association of COVID-19 positivity, problems attending medical appointments during the outbreak and subjective experience of MS progression during the pandemic with emotional variables.

Depression	B	SE	β	*t*	*Sig.*
Fear to COVID-19	.456	.177	.171	2.568	.011*
Positive to COVID-19	1.141	1.986	-.038	-.574	.56
Problems attending medical appointments	1.260	.709	.118	1.777	.007*
Disease progression during the pandemic (subjective experience)	3.994	.833	.320	4.796	.001**
Anxiety					
Fear to COVID-19	.171	.072	.132	2.383	.018*
Positive to COVID-19	8.065	.803	.559	10.041	.001**
Problems attending medical appointments	.560	.287	.109	1.954	.052
Disease progression during the pandemic (subjective experience)	1.157	.337	.191	3.436	.001**

Note.SE(Standard Error) *($p < .05$), **($p < .001$)

4. Discussion

The first objective of our study was to explore the reactions of anxiety, depression and fear of COVID-19 in a group of PwMS. Additionally, we explored if testing positive to COVID-19, fear of COVID-19, problems to attend medical appointments during the outbreak and subjective experience of MS progression during the pandemic, predicts the anxiety and depression reactions in PwMS.

Our results showed that PwMS who were positive for COVID-19 reported higher levels of fear of COVID-19 and also higher levels of anxiety compared to non-positive patients. In our study those patients who had difficulties attending their medical appointments during the outbreak, showed higher levels of depression and anxiety, compared to those who did not have problems to visit their neurologist. The levels of anxiety and depression were also higher among patients who manifested the subjective experience of MS disease progression.

To date, studies that have explored the psychological impact of COVID-19 in PwMS recovered from infection have been limited. However, the results of studies conducted in the general population suggested that mental health problems in people recovered from Covid-19 ranges between 10% and 35% (Khademi et al., 2021; Kong et al., 2020). For example, a recent study of hospitalized patients with COVID-19 found that 34.7 and 28.4% of patients had symptoms of anxiety and depression, respectively (Kong et al., 2020).

Overall, there are recent studies that have also revealed a negative mental health impact in PwMS that have not tested positive during the current pandemic. These studies found a higher prevalence of depression and anxiety than usual (Motolese et al., 2020; Talaat et al., 2020).

For example, a recent study reported elevated levels of anxiety, depression, and distress in PwMS compared to their caregivers and a group of controls from the general population (Talaat et al., 2020). Among these patients, an increase in the number of relapses was

observed and also a poor knowledge about the risk factors related to COVID-19 infection.

Another study carried out in Italy also reported a higher burden of depressive symptoms, a worse sleep quality and perceived an increase in fatigue level in PwMS (Motolese et al., 2020). Furthermore, 20% of the study participants reported a worsening of MS disease severity, in particular, sensory disturbances and fatigue that were positively related to fatigue and to sleep problems.

This increase in anxiety, depression and fear reactions in patients with multiple sclerosis can be related to many factors. In the general population, physical distancing, economic tensions, labor difficulties, quarantines, are some of the causes related to worse mental health (Passavanti et al., 2021). However, PwMS have additional concerns that are directly related to the characteristics of the disease (Ahadi et al., 2020).

For example, in our study, the reactions of fear of COVID-19, having been positive to COVID-19, problems attending medical appointments, and subjective experience of MS disease progression showed a high association with the negative impact of the pandemic on mental health of PwMS.

In the case of fear of COVID-19, a recent study reported a positive association between this variable and depression and anxiety reactions in a sample of Iranian PwMS (Ramezani et al., 2021). In Iranian patients, fear of COVID-19 was associated with a history of MS relapse during the preceding year, and with a recent corticosteroids treatment (indicating a recent disease activity).

The pandemic has also caused a disruption in medical services, which explains why difficulties in accessing consultations increase anxiety levels in our sample. This result has also been confirmed by a study that explored the effect of the disruptions in care services experienced by PwMS in Italy in a large sample of 2722 patients (Manacorda et al., 2020). In this study, it was found that in severely disabled MS patients, the lack of usual care and support often put additional burden and stress (Manacorda et al., 2020). According to the authors, many respondents indicated that they had to decide between receiving care and protecting themselves against the risk of infection, potentially undermining the mental health of patients.

Finally, it was also found that the subjective experience of MS disease progression, during the pandemic, was significantly associated with higher levels of depression and anxiety in our PwMS sample. The subjective experience of MS disease progression is closely related to the fear of disease progression, which is a meaningful emotional stressor in patients with MS, especially in those with depression (Nielsen et al., 2018).

According to this, the current epidemiological scenario could amplify the main source of anxiety in patients with Multiple sclerosis, that is, the relapse itself. (Khatibi et al., 2020). Increased fear of relapse can also cause an increase in somatization, which has recently been reported in patients with autoimmune diseases (Louvardi et al., 2020). The increase in somatization also implies an increase in the levels of distress among patients with autoimmune diseases during the current COVID-19 outbreak.

On this subject, a recent study in the general population, using the machine learning approach, reported that somatization was among the predictors of psychological distress during COVID-19, and it was the main predictor of anxiety, depression and stress reactions (Prout et al., 2020). We do not rule out the possibility that there are patients with a real worsening of the disease in our sample, in fact, there are studies that reported an increase in the severity of MS during the pandemic, in particular, sensory alterations and fatigue (Motolese et al., 2020). However, if a patient has a subjective experience of MS disease progression and that perception causes an increase in their levels of anxiety, depression and distress, there is already a negative impact, despite the progression is real or not. If patients consider that the experience of the disease progression is real, that experience will be real at least in its consequences.

Although the impacts of COVID-19 are still largely unknown and debates persist about its effect on the overall health of PwMS (Krieger, 2020; Preziosa et al., 2020), the management of mental health reactions in these patients should be a priority for health systems around the world.

This study has some limitations that we have to address. In the first place, our study did not include measurements of the emotional variables prior to the impact of COVID-19, which does not allow us to define whether the current psychological reactions are directly related to the current epidemiological situation. Second, the cross-sectional design did not allow for empirically establishing causal relationships between predictor and outcome variables. Additionally, our research does not control for variables related to the level of disability, which may have a direct effect on the levels of psychological distress. Additionally, our study did not include a control group, so it is difficult to estimate whether the levels of depression, anxiety or fear of COVID-19 are higher or lower than those reported by the general population.

In conclusion, our results showed that PwMS, who were positive for COVID-19, reported higher levels of fear of COVID-19, and also higher levels of anxiety and depression. Additionally, we verified that fear of COVID-19, having been positive to COVID-19, problems attending medical appointments, and subjective experience of MS disease progression, showed a high association with the negative impact of the pandemic on the mental health of PwMS. These results are an alert of the importance of offering psychological care to PwMS during the current outbreak, whether they were positive for COVID-19 or not.

Credit Author Statement

Concept - All authors; Design- All authors; Supervision- YBP, RMJM; Resource - All authors; Materials - All authors; Data Collection - All authors; Analysis and / or Interpretation - YBP, RMJM,ZFF; Literature Search - All authors; Writing - YBP; Critical reviews – YBP, RMJM.

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Declaration of Competing Interest

The authors have no conflicts of interest

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