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Fear of re-infection, relapse, and anxiety during COVID-19 pandemic in patients with multiple sclerosis: A multi-center study

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Abstract
Background: Fear of relapse and re-infection during the coronavirus disease 2019 (COVID-19) pandemic can affect people with chronic relapsing diseases, such as multiple sclerosis (MS). We evaluated fear of re-infection, anxiety, and relapse during the COVID-19 pandemic in Iranian people with MS.

Methods: This multicenter, cross-sectional study was performed in the MS clinic of Sina Hospital, Tehran, Iran, and Hakim Private Hospital, Isfahan, Iran, between January and April 2022. We asked the participants to fill out validated Persian versions of Fear of Relapse Scale (FoR), and Beck Anxiety Inventory (BAI) questionnaires and answer a binary question about their fear of getting reinfected with COVID-19. Results were reported as mean ± standard deviation (SD) for continuous variables or frequencies for categorical variables. For continuous variables which did not have a normal distribution, we reported the median and interquartile range (IQR). Spearman correlation coefficient between anxiety score and FoR score was calculated. An independent samples t-test was used to compare continuous variables.

Results: Three hundred and sixty-eight patients participated in this study. The median scores of FoR and BAI were 49.7 and 34.3, respectively. Fifty-three had new relapses in their last infection.

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Thirty-six percent of the patients had a fear of getting COVID-19 again, and 43% had a fear of relapse during infection. Three hundred and twenty-three had two doses of COVID-19 vaccine; the most frequent type of vaccine was Sinopharm. There was a significant difference between the median FoR scores among patients with and without relapse during the last COVID-19. There was also a significant positive correlation between anxiety score and FoR (r = 0.49, P < 0.001).

Conclusion: More than one-third of enrolled cases had fear of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) re-infection. Patients who experienced exacerbation of symptoms even in the form of relapse or pseudo relapse (possible clinical relapse) had a higher fear of infection.

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), more commonly affecting women and young adults.[1] The most common form of the disease is relapsing-remitting MS (RRMS), which affects patient's quality of life (QOL) by the development of episodic new neurological symptoms.[2,3] Coronavirus disease 2019 (COVID-19) is still in the pandemic stage. At first, it was suggested that patients with MS were at higher risk of COVID-19 infection, but it was not confirmed.[4] A systematic review and meta-analysis showed that the pooled prevalence of COVID-19 in patients with MS was 4% (the range in the Iranian population was between 1%-5%).[5-8]

Patients with MS who receive immunosuppressive or immune-modulatory medications may suffer from anxiety and other psychological comorbidities during the pandemic.

Anxiety is common in MS, and fear is the core part of anxious thoughts, especially in the relapse phases.[9] A study in Iran showed that anxiety positively correlated with the fear of relapse in MS, and sex was an independent predictor of fear of relapse.[10]

Infections may result in MS relapses. As getting COVID-19 does not completely protect the person against re-infections (usually with new variants), patients with MS can be more concerned about the risks of experiencing relapses during the pandemic or being re-infected with COVID-19.[11] These fears can worsen the comorbid anxiety symptoms in these patient. We performed a multicenter study to understand the prevalence and severity of fear of relapse and fear of reinfection and their association with the symptoms of anxiety in Iranian patients with MS.

Materials and Methods

This multicenter, cross-sectional study was done in the MS clinic of Sina Hospital (affiliated hospital of Tehran University of Medical Sciences, Tehran, Iran) and Hakim Private Clinic, Isfahan, Iran, between January and April 2022.

Inclusion criteria were: age of more than 18 years, RRMS, and a documented COVID-19 infection before the study (a positive nucleic acid amplification test). Exclusion criteria were: secondary progressive MS (SPMS) or primary progressive MS (PPMS) and age less than 18 years.

All particpants signed an informed consent form before entering the study. The study was approved by the Ethics Committee of Tehran University of Medical Sciences (ethics code: IR.TUMS.NI.REC.1400.065).

Patients' demographics (age, sex, and education), disease duration, and Expanded Disability Status Scale (EDSS) were obtained from the clinic records. Participants completed questionnaires regarding fear of re-infection, fear of developing relapse during COVID-19 infection, being anxious about the cessation of medications during re-infection, type of COVID-19 vaccine they got, if they had re-infection after vaccination, if they got both doses of vaccination, and time since the last infection.

We also asked the participants to fill out validated Persian versions of Fear of Relapse Scale (FoR) and Beck Anxiety Inventory (BAI) questionnaires.

FoR includes 26 questions each scored on a five-point Likert scale including 1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = always. The total score is the sum of scores of all questions. Higher scores denote higher fear of relapse.

BAI includes 21 questions, each rating from 0 to 3. The total score is the sum of scores of all items. Higher scores denote more severe anxiety.

Data were analyzed using the SPSS software (version 22, IBM Corporation, Armonk, NY, USA). Results were reported as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables or frequencies for categorical variables.

Spearman correlation coefficient between anxiety score and FoR score was calculated. A Mann-Whitney U test was used to compare continuous variables. A P-value less than 0.05 was considered significant.

Results

Three hundred and sixty-eight patients participated in this study. The mean age and mean disease duration were 37.4 ± 8.7 and 7.7 ± 5.5 years, respectively (Table 1).

The median and IQR of FoR and BAI were 49.7 (20.5) and 34.3 (12.4), respectively.

Thirty-six percent of the patients had a fear of getting COVID-19 again, and 43% had a fear of relapse during infection. Fifty-three patients had new relapses in their last infection.

Three hundred and twenty-three had got two doses of COVID-19 vaccine and the most frequent type of vaccine was Sinopharm. The most common reason for fear of re-infection was fear of transmitting the virus to others (Table 2).

Table 1. Demographic and disease-related characteristics of the enrolled participants

Variable	Value
Age (year) (mean ± SD)	37.4 ± 8.7
Disease duration (year) (mean ± SD)	7.7 ± 5.5
Education (year) (mean ± SD)	14.4 ± 3.3
EDSS [median (IQR)]	1.5 (2.5)
Sex [n (%)]	
Women	299 (81.3)
Men	69 (18.8)

EDSS: Expanded Disability Status Scale; SD: Standard deviation; IQR: Interquartile range

Table 2. Mean scores of questionnaires and frequency of categorical questions

Variable	Value
FoR (mean ± SD)	49.7 ± 20.5
BAI (mean ± SD)	34.3 ± 12.4
Time since the last infection (mean ± SD)	12.2 ± 8.5
Do you fear of getting COVID-19 again? [n (%)]	14.4 ± 3.3
Yes	133 (36.1)
No	253 (63.9)
Do you have fear of developing relapse during re-infection? [n (%)]	
Yes	160 (43.5)
No	208 (56.5)
Did you develop relapse during the last infection? [n (%)]	
Yes	53 (14.4)
No	315 (85.6)
Had you been hospitalized during your last COVID-19? [n (%)]	
Yes	59 (16.0)
No	309 (84.0)
Did you discontinue your MS medication during the last COVID-19 disease? [n (%)]	
Yes	59 (16.0)
No	309 (84.0)
Do you have fear of discontinuation of your MS medications due to COVID-19? [n (%)]	
Yes	110 (29.9)
No	258 (70.1)
Have you got two doses of SARS-CoV-2 vaccine? [n (%)]	
Yes	323 (87.8)
No	45 (12.2)
Type of vaccine [n (%)]	
Oxford/AstraZeneca (ChAdOx1-S)	24 (6.5)
Sinopharm	296 (80.4)
Sputnik	5 (1.4)
COVIran Barekat	7 (1.9)
Others	4 (1.1)
Have you had SARS-CoV-2 infection after vaccination? [n (%)]	
Yes	121 (32.9)
No	247 (67.1)
The reason of SARS-CoV-2 infection fear [n (%)]	
Medication discontinuation	11 (3.0)
MS-related relapse	87 (23.6)
Hospitalization	57 (15.5)
Transmission of the virus to the others	140 (38.0)

FoR: Fear of Relapse Scale; BAI: Beck Anxiety Inventory; COVID-19: Coronavirus disease 2019; SD: Standard deviation; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MS: Multiple sclerosis

There was a significant difference in mean FoR score among the groups with and without relapse during the last COVID-19 (58.8 ± 24.0 vs. 48.1 ± 19.4, P = 0.003).

There was also a significant positive correlation between anxiety score and FoR (rho = 0.49, P < 0.001).

Discussion

To our knowledge, this is the first study that evaluated the fear of COVID-19 re-infection in people with MS and a history of COVID-19 infection. The results demonstrated that more than one-third of included patients had a fear of re-infection, and the most common reason for fear was transmitting the virus to others.

We also showed that 43% had fear of developing relapse during the re-infection and FoR was significantly higher in cases who had MS-related relapse in their last infection.

This shows that MS-related relapses may result in concern among patients with RRMS after COVID-19 infection. A recent study in Iran showed that more than two-thirds of Iranian subjects with MS were worried about developing relapses after COVID-19 infection.[12] Infections exacerbate the MS-related symptoms (pseudo-relapses) and may lead to true relapses. A study conducted in Argentina evaluated 41 patients with MS who had COVID-19. The authors reported that 25 patients had exacerbation of the symptoms, and three cases had developed relapse during the infection.[13]

Literature shows that viral infections, such as picornavirus, influenza, adenovirus, and cytomegalovirus, can exacerbate MS-related symptoms and may result in true MS relapses.[13]

Most patients in this study (88%) received two doses of a COVID-19 vaccine and the most common type of vaccine was Sinopharm. A recent systematic review and meta-analysis showed that nearly two-thirds of patients with MS were willing to get their COVID-19 vaccines, and only 2% were unwilling.[14] This higher interest in vacciantion is probably explainable by the fact that most patients are under the treatment with immunosuppressive or immunomodulatory agents and vaccination will help to reduce the rate of hospitalization and severe infections.[15,16]

We found that one-third of the participants had COVID-19 after vaccination, which is higher than the rated rate. Ghadiri et al. enrolled 692 patients with MS who completed a course of vaccination (the most frequent vaccine type was Sinopharm) and reported 13.6% infection after complete immunization.[17]

Patients with MS in Iran were among the people who had vaccination earlier than the general population and re-infection after vaccination could be due to the effects of MS disease-modifying drugs (such as anti-CD20 medications) and lower efficacy of vaccines in these patients.[17]

We found a significant positive correlation between anxiety and FoR and a significantly higher score of FoR in patients with relapses during the last infection.

MS relapses are not predictable. Relapses impair the QOL, and impose anxiety and distress on the patients with MS. It has been shown that the QOL scores are significantly reduced during the relapses in subjects with MS.[18] Therefore, factors that may predict relpases are important and should be considered by physicians.

This study had several strengths. First, it was a multi-center study, conducted in both academic and private settings. Second, the sample size was relatively large. Third, we evaluated anxiety simultaneously.

The study has several limitations. We did not collect the DMT profile of the patients. We also did not have the data regarding the post-vaccination antibody status of the participants. As relapse was based on the patient's reports, we could not differentiate relapse and pseudo-relapse.

Conclusion

More than one-third of enrolled cases had fear of SARS-CoV-2 re-infection. Patients who experienced exacerbation of symptoms even in the form of relapse or pseudo relapse (possible clinical relapse) had a higher fear of infection.

Conflict of Interests

The authors declare no conflict of interest in this study.

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