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Original article

COVID-19 and its implications on the clinico-radiological course of multiple sclerosis: A case–control study

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ABSTRACT

Background: Multiple sclerosis (MS) is an immune-mediated disease that has been related to several risk factors such as various viral infections. We carried out this study in order to establish a relationship between COVID-19 infection and MS severity.
Methods: In a case–control study, we recruited patients with relapsing–remitting multiple sclerosis (RRMS). Patients were divided into two groups based on positive COVID-19 PCR at the end of the enrollment phase. Each patient was prospectively followed for 12 months. Demographical, clinical, and past medical history were collected during routine clinical practice. Assessments were performed every six months; MRI was performed at enrollment and 12 months later.
Results: Three hundred and sixty-two patients participated in this study. MS patients with COVID-19 infection had significantly higher increases in the number of MRI lesions (p: 0.019, OR(CI): 6.37(1.54–26.34)) and EDSS scores (p: 0.017), but no difference was found in total annual relapses or relapse rates. COVID-19 infections were positively correlated with EDSS progression (p: 0.02) and the number of new MRI lesions (p: 0.004) and predicted the likelihood of the number of new MRI lesions by an odds of 5.92 (p: 0.018).
Conclusion: COVID-19 may lead to higher disability scores in the RRMS population and is associated with developing new Gd-enhancing lesions in MRI imaging. However, no difference was observed between the groups regarding the number of relapses during follow-up.

COVID-19 y sus implicaciones en el curso clínico-radiológico de la esclerosis múltiple: un estudio de casos y controles

Palabras clave:
COVID-19
Esclerosis múltiple
Recaída
Progresión
EDSS
Realce de lesiones

RESUMEN

Antecedentes: La esclerosis múltiple (EM) es una enfermedad inmunomediada que se ha relacionado con varios factores de riesgo, como diversas infecciones virales. Realizamos este estudio para establecer una relación entre la infección por COVID-19 y la gravedad de la EM.
Métodos: En un estudio de casos y controles, reclutamos pacientes con esclerosis múltiple remitente-recurrente (EMRR). Los pacientes se dividieron en dos grupos según la PCR positiva para COVID-19 al final de la fase de inscripción. Cada paciente fue seguido prospectivamente durante 12 meses. Los antecedentes

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demográficos, clínicos y médicos anteriores se recogieron durante la práctica clínica habitual. Las evaluaciones se realizaron cada 6 meses. La resonancia magnética se realizó en el momento de la inscripción y 12 meses después.
Resultados: Trescientos sesenta y dos pacientes participaron en este estudio. Los pacientes con EM con infección por COVID-19 tuvieron aumentos significativamente más altos en el número de lesiones de resonancia magnética (p = 0,019; OR = 6,37 [IC 95%: 1,54-26,34]) y puntajes EDSS (p = 0,017), pero no se encontraron diferencias en el total de recaídas anuales o en las tasas de recaída. Las infecciones por COVID-19 se correlacionaron positivamente con la progresión de EDSS (p = 0,02) y la cantidad de nuevas lesiones en la resonancia magnética (p = 0,004) y predijeron la probabilidad de la cantidad de nuevas lesiones en la resonancia magnética con una probabilidad de 5,92 (p = 0,018).
Conclusión: COVID-19 puede conducir a puntajes de discapacidad más altos en la población de EMRR y está asociado con el desarrollo de nuevas lesiones realzadas con Gd en imágenes de resonancia magnética. Sin embargo, no se observó diferencia entre los grupos en cuanto al número de recaídas durante el seguimiento.

Introduction

Multiple sclerosis (MS) is an immune-mediated condition that results in demyelination and axonal injury (progressive neurodegeneration) in the central nervous system (CNS).[1,2] The relapsing–remitting form of multiple sclerosis (RRMS), the most common type of the disease, is characterized by periodic bouts of acute exacerbations followed by periods of relative clinical stability.[3] The neurological impairment in MS is usually assessed using an expanded disability status scale (EDSS), which evaluates the different neurological domains that might be comprised by the disease.[4] Magnetic resonance imaging (MRI) is the preferred imaging technique for MS diagnosis and follow-up. The number of lesions and presence of brain atrophy could be seen with MRI.[5] Several risk factors have been suggested for MS susceptibility and increased attack rates, including female sex, genetic, and environmental factors. Several lines of evidence suggest that the immune system plays an integral and perhaps defining role in the development of MS[6]; alternative theories of MS pathogenesis state that a chronic viral infection may contribute to its pathogenesis.[7] A foreign antigen, such as a virus or bacteria, seems to provide an antigenic trigger for MS autoimmunity through molecular mimicry.[8] However, the cause of MS remains unknown.[9]

COVID-19 could involve many organs and present with numerous manifestations from asymptomatic to death.[10] Neurological symptoms are a less likely presentation of COVID-19, including headache, dizziness, myalgia, anosmia, dysgeusia, seizure, Guillain-Barré syndrome, encephalitis, and acutely demyelinating encephalomyelitis, optic neuritis, and MS.[11–15] Some reports suggest an association between MS and other infections like the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[12] Simultaneous involvement of two mechanisms has been proposed for this concurrence; first, an enhanced inflammatory response, which results in blood-brain barrier dysfunction and subsequent immune cell migration into the central nervous system (CNS), and the second is a direct neuroinvasion.[16–18]

COVID-19 has been examined to determine whether it affects the natural course of RRMS since the previous studies were inconclusive. The study aimed to determine how the attack rate, disability status, clinical presentation, and neuroimaging findings changed during the COVID-19 pandemic in a cohort of Iranian men and women.

Material and methods

Study design

This is a case–control study conducted at the tertiary MS Center of Sina Hospital in Tehran based on the MS-COVID-19 registry system of Iran[19] (The Nationwide MS Registry of Iran (NMSRI) is a dynamic, follow-up based registry.[20]) The case group was defined as MS patients with a positive COVID-19 PCR at the end of the enrollment phase. The control group included the other MS patients who didn't infect by the COVID-19 virus. The enrollment phase runs from 1 May 2020 to 25 July 2020. We enrolled patients with (1) age between 20 and 65 years, (2) a definitive diagnosis of RRMS per the revised McDonald criteria by a neurologist (AN Moghadasi),[21] and (3) having a magnetic resonance imaging (MRI) scan. Exclusion criteria were as follows: (1) history of a documented COVID-19 diagnosis by PCR and (2) patients who presented severe disease that may result in death, (3) the presence of a confounding underlying condition that would invalidate MS evaluation like other neurologic diseases, anoxic brain injury, or intracranial neurotrauma and (4) Patients who have discontinued or interrupted their MS regimen for more than a week. Informed consent was obtained from all patients after fully informing them of our research process and purpose and the medical ethics committee of our hospital approved the study protocol (IR.AJAUMS.REC.1399.222).

A study center staff member instructed the patients to call when they felt sick or experienced neurological impairment and visit the outpatient clinic every six months (specific dates were set for each patient). After a suspected infection or exacerbation, an additional outpatient clinic visit was scheduled within three days. In the case of suspected infection (worsening of cold symptoms, including nasal congestion, nasal discharge, fever, cough, myalgia, and headache), Nasal swab specimens were collected in duplicate to detect SARS-COV-2 (COVID-19) by reverse transcriptase-polymerase chain reaction (RT-PCR); In the course of the study, patients positive for COVID-19 were excluded, and their information was not included in the final analysis.[19] Patients kept a weekly diary to ensure that infections and neurological complaints were being reported to the clinician throughout the entire study period. Each patient was prospectively followed for 12 months.

The case group included 71 MS patients with a positive COVID-19 PCR at the end of the enrollment phase, and the control group included the other 496 patients. A total of 19 patients from the case group and 186 patients from the control group were withdrawn during the study due to positive COVID-19 PCR's, unwillingness to participate, or inaccurate reporting of suspected infections or exacerbations.

Baseline assessment

Demographic characteristics (age, BMI, smoking, and marital status), clinical disability (assessed by the Expanded Disability Status Scale (EDSS)), and past medical history (underlying diseases and family history of MS) were collected as part of routine clinical practice with assessments scheduled every six months. All patients

underwent an MRI scan at enrollment phase. A second scan was performed at the third outpatient visit (12 months after the investigation began) to non-excluded patients. All patients had their EDSS re-evaluated in the course of a twelve-month follow-up, but those who had exacerbations or hospitalizations around the end of the study were re-evaluated following a month of improvement or stabilization.

Definitions

An exacerbation of multiple sclerosis was defined as developing a new neurological symptom or worsening an existing symptom or symptoms attributable to multiple sclerosis lasting > 24 h after a period of ≥30 days of improvement or stability.[22] Neurological deterioration temporarily associated with the occurrence of fever was not considered as exacerbation. The state of COVID-19 vaccination was not assessed as a variable in this study because only eighteen patients got the first dose of COVID-19 in the last three months of follow-up.

MRI protocol

Our brain MR imaging protocol includes T1-weighted, T2-FLAIR, T2-weighted, post-single-dose gadolinium-enhanced T1-weighted sequences, and a DWI sequence.

A 1.5 T MRI system (Philips NT, Best, The Netherlands) was used to obtain SE T1-weighted pre- and post-Gd-DTPA (diethylenetriaminepentaacetic acid) images [5 mm slices with 0.5 mm gap, TR (repetition time) = 450 ms, TE (echo time) = 15 ms, FOV (field of view) = 230 mm, matrix = 256 × 256]; the dose of Gd-DTPA was 0.1 mmol/kg. The numbers of enhancing lesions were measured in all scans performed.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were described in frequency and percentage. Preliminary analyses showed no outliers, as assessed by a boxplot. The variables were tested for normality using the Shapiro–Wilk's test; Continuous and parametric data with a normal distribution (Shapiro–Wilk's test ($p > 0.05$)) were compared between two independent groups with an independent *t*-test. In contrast, categorical data were analyzed with the chi-squared test followed by Fischer's exact test. Variables without normal distribution (Shapiro–Wilk's test ($p < 0.05$)) and the nonparametric data were compared between two independent groups with the Mann–Whitney *U* test; the Man–Whitney *U* test assumption of equal distribution were tested by using Levene's test for equality of variances based on median and with an adjusted degree of freedom. Spearman's rank correlation coefficient was applied to detect correlations between clinical and medical variables and COVID-19 exposure in MS patients. According to Cohen 1988,[23] the effect size of correlations was interpreted as small (0.1–0.3), medium (0.3–0.5), or large (>0.5).

Binomial logistic regression was applied to evaluate the predictive power of COVID-19 for new MRI enhancements (binary; yes, or no) and relapse (binary; yes, or no), separately. Each regression model was adjusted for age, sex, baseline EDSS, BMI, disease duration, underlying diseases, and MS family history. Regression coefficients with 95% confidence intervals (CI) and the corresponding p-values were calculated for each independent variable. The Hosmer and Lemeshow test was used to assess the fit of the risk prediction models, and the Linearity of continuous variables for the logit of the dependent variable was assessed with the Box–Tidwell procedure.

Multiple linear regressions were run to predict the increases in EDSS scores from COVID-19 exposure. The regression model was adjusted for age, sex, baseline EDSS, BMI, disease duration, underlying diseases, and MS family history. Linearity was found in partial regression plots and residuals against the predicted values. A Durbin–Watson statistic verified the independence of residuals, and homoscedasticity was confirmed by visual inspection of a plot of residuals versus unstandardized predicted values. No evidence of multicollinearity was found, given that the tolerance values were higher than 0.2. The statistical analysis was performed using SPSS version 26 (SPSS Inc., Chicago, IL). A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The case group included MS patients with a positive COVID-19 PCR at the end of the enrollment phase (*N*:71), and the control group included the other 496 patients who did not present SARS-COV-2 infection.

Considering 205 patients excluded from the study, a total of three hundred sixty-two patients were entered (52 cases and 310 controls) the final analysis; Three hundred twelve of the subjects (86%) were female, similar to the general RRMS population. Thirty-seven patients (11%) of the control group required hospitalization at least once, which was not statistically significant compared to seven patients (13%) of the case group. The average age was 38.3 years (range 20–65 years), and the average disease duration from diagnosis was 5.7 years (range 2–28 years). The median (IQR) of initial EDSS assessment was 1 (1–3), average numbers (SD) of T1 gadolinium enhancing lesions and T2 lesion volume (mm3 × 103) at entry were 0.50 (0.32) and 16.5 (14.5), respectively, and the average number of exacerbations in the two years preceding enrollment was 1.8 (Table 1).

Outcomes

Table 2 compares MRI lesions, EDSS and relapses according to two groups of cases and controls prospectively followed for a year. MS patients with COVID-19 positive PCR had significantly higher increases in MRI lesions (OR: 6.37, CI: 1.54–26.34, p: 0.017) and EDSS (OR: 0.38, CI: 0.06–0.69, p: 0.019) compared with MS patients with COVID-19 negative PCR, but no difference was found in relapses (OR: 2.24, CI: 0.84–5.99, p: 0.119).

EDSS increase

We used a multiple regression model to predict how the EDSS increase would be affected by the SARS-COV-2 infection. The regression model was adjusted for age, sex, baseline EDSS, BMI, disease duration, underlying diseases, and MS family history. The SARS-COV-2 infection was statistically significant in predicting patient's EDSS increase (p: 0.026). The regression coefficients are reported in Table 3.

New MRI lesions and relapses

New MRI lesions showed significant correlation with COVID-19 (Spearman's coefficient = 0.15, p: 0.004). In contrast, the chance of relapse in one year didn't correlate with COVID-19 (Spearman's coefficient = 0.08, p: 0.098).

Two models were used to estimate the predictive value of COVID-19 for the occurrence of new MRI lesions and the chance of relapse in one year. Each regression model was adjusted for age, sex, baseline EDSS, BMI, disease duration, underlying diseases, and MS family history.

Table 1
Demographic and medical characteristics of participants.

Characteristic	Cases (MS patients with COVID-19) *N* (%)	Controls (MS patients without COVID-19) *N* (%)	Characteristic	Cases (MS patients with COVID-19) *N* (%)	Controls (MS patients without COVID-19) *N* (%)
Sex			*Underlying diseases*		
Male	13 (26%)	73 (12.5%)	Hypertension	12 (3.9%)	2 (3.8%)
Female	39 (74%)	273 (87.5%)	CAD	7 (2.3%)	1 (1.9%)
Age (Mean (SD))	37.6 (9.23)	38.4 (9.05)	Diabetes	10 (3.2%)	5 (9.6%)
Smoking			Pulmonary disease	5 (1.6%)	1 (1.9%)
Smoker	11 (21.2%)	52 (16.8%)	Interferon beta 1a	6 (11.5%)	65 (21%)
Non-smoker	41 (78.8%)	258 (83.2%)	*Disease modifying therapies*		
BMI			Interferon beta 1b	2 (3.8%)	10 (3.2%)
<18.5	1 (1.9%)	7 (2.3%)	Glatiramer acetate	7 (13.5%)	58 (18.7%)
18.5–24.9	23 (44.2%)	156 (50.7%)	Fingolimod	4 (7.7%)	53 (17.1%)
25–29.9	24 (46.2%)	123 (39.9%)	Natalizumab	2 (3.8%)	6 (1.9%)
≥30	4 (7.7%)	22 (7.1%)	Rituximab	30 (57.8%)	110 (35.5%)
Family history of MS			Triflunomide	0	1 (0.3%)
Yes	11 (21.2%)	65 (21%)	Dimethyl Fumarate	1 (1.9%)	7 (2.3%)
No	41 (78.8%)	245 (79%)	*Baseline EDSS (Mean (SD))*	2.07 (1.87)	1.95 (1.87)
Disease duration (months)			*Baseline MRI lesions (Mean (SD))*	0.47 (0.30)	0.51 (0.33)
<60	12 (23.1%)	60 (19.4%)			
61–120	24 (46.2%)	93 (30%)			
>120	16 (30.7%)	157 (50.6%)			
Total	52 (14.4%)	310 (85.6%)			

SD: standard deviation, BMI: body mass index, MS: multiple sclerosis, CAD: coronary artery disease, EDSS: expanded disability status scale, MRI: Magnetic Resonance Imaging.

Table 2
Comparison of outcome measures between case and control groups.

	MS patients		*p*-Value	OR (CI 95%)
	Control	COVID-19		
New enhancement in MRI				
No	306	48	0.017[+]	6.37 (1.54–26.34)
Yes	4	4		
Relapse				
No	293	46	0.119[+]	2.24 (0.84–5.99)
Yes	17	6		
No. of relapses(Mean(SD))	0.85 (1.05)	0.98 (0.98)	0.261	1.12[*]
EDSS increase(Mean(SD))	0.17 (1.11)	0.55 (0.80)	0.019	0.38 (0.06–0.69)[#]
Total	310	52		

[+] Fischer's exact.
[*] *Z* score (Mann–Whitney *U*).
[#] Mean difference (CI 95%) (Independent *T*-test).
MS: multiple sclerosis, MRI: magnetic resonance imaging, No: number, EDSS: expanded disability status scale, SD: standard deviation, OR: odds ratio, CI: confidence interval.

Table 3
Multiple linear regression analysis for EDSS increase.

Condition	Variable	Spearman's correlation		*B*[*] (CI 95%)	*p*-Value	*R* square	Durbin–Watson
		Coefficient	*p*-Value				
EDSS increase	COVID-19	0.124	0.009	0.38 (0.04–0.69)	0.026		
Model summary					0.07	0.020	1.77

EDSS: expanded disability status scale, CI: confidence interval.
[*] Unstandardized beta coefficient.

The first model (New enhancement in MRI) worked well (omnibus tests of model coefficient: χ^2-value = 432, $p < 0.0001$, Nagelkerke R Square = 0.93) and fit (Hosmer–Lemeshow: χ^2-value = 7.98, p: 0.43). Based on regression coefficients, COVID-19 increased the likelihood of new MRI lesions by an odds of 5.92 (p: 0.018).

The second model (Relapse) also worked well (omnibus tests of model coefficient: χ^2-value = 342, $p < 0.0001$, Nagelkerke R Square = 0.81) and fit (Hosmer–Lemeshow: χ^2-value = 5.17, p: 0.73). In contrast, COVID-19 (p: 0.079) was not a valuable predictor for the chance of relapse in one year (Table 4).

Discussion

In this study, we aimed to find an answer to how COVID-19 can affect the natural course of RRMS. We conducted a prospective, case–control study to assess the relapse rate, the degree of disability based on the EDSS index, and the new MRI lesions changed after COVID-19. Based on the results, COVID-19 infections were associated with an increase in enhancing lesions in MRIs and a higher EDSS score among RRMS patients over one year. To the best of our knowledge, no previous study has investigated the effects of COVID-19 infection on EDSS scores in MS patients.

Table 4
Summary of binary logistic regression models for predicting new enhancement in MRI and Relapse rate based on COVID-19.

Variable	Condition	Spearman's Correlation		Wald	OR	95% CI	*p*-Value	HS Value
		Coefficient	*p*-Value					
COVID-19	New enhancement in MRI*	0.153	0.004	5.56	5.92	1.35–25.94	0.018	0.43
	Relapse	0.087	0.098	3.08	2.56	0.89–7.31	0.079	0.75

* Statistically significant *p*-value with statistically non-significant Hosmer–Lemeshow test (Model Fitness).
MRI: magnetic resonance imaging, OR: odds ratio(Exp(*B*)), CI: confidence interval, HS: Hosmer–Lemeshow test.

Still, some studies on other infections have reported similar results, suggesting that systemic infections cause more severe and sustained exacerbations.[24,25]

Sibley's "at-risk" period[26] for MS attacks was established to evaluate the impact of infection on MS exacerbation. This period begins two weeks before infection and ends five weeks after the infection. Our study did not measure the at-risk period, so our findings showing that COVID-19 infection did not affect the overall annual attack rate do not imply that COVID-19 does not affect the chances of an attack during the acute phase of the disease. Meanwhile, the results indicate that overall relapse rates of MS patients are not affected by the COVID-19 infection.

Molecular mimicry, epitope spreading, and bystander activation are some mechanisms contributing to dysregulated immune responses after infections.[27,28] Toll-like receptors (TLRs), which are important parts of the innate defense system, have been previously linked to the pathogenesis of several autoimmune diseases and may also be involved in triggering MS exacerbations.[29] TLRs' role in COVID-19 induced cytokine storm and subsequent demyelinating neuropathy has been noted in some studies.[30,31] It has also been demonstrated that the activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome and the following rise in IL-1β and IL-18 is a major risk factor for MS progression.[32] Interestingly, COVID-19 infection can induce a rapid expression of NLRP3, leading to inflammatory cytokines' release. Thus, this mechanism might serve as a possible explanation for the observed CNS involvements.[33] Increased blood-brain barrier (BBB) permeability is an important step in developing Gd-enhancing lesions.[34–36] It has been demonstrated that infections can upregulate the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which leads to disruption of BBB and stimulation of microglial cells, which in turn facilitates the migration of activated T cells into the central nervous system (CNS).[37,38]

Similar to the observations in our study, the association between infectious diseases and the development of MRI enhancements have also been mentioned in several articles.[24,39] In contrast, a prospective cohort study has documented that, while viral infections lead to an increased rate of MS relapse, these relapses are not accompanied by the formation of new Gd-enhancing lesions.[25] Some studies suggest parasitical infections and microbial agents such as Helicobacter pylori might decrease MS exacerbations and associated disability, preventing new enhancing lesions in MRI.[40–43]

The higher risk of disability and morbidity after COVID-19 infection in MS patients, as demonstrated by an increase in EDSS score in this study, highlights the importance of disease prevention strategies in this population. However, the controversy and the scarcity of studies regarding this subject require additional studies to be carried out to ascertain the reproducibility of our results.

This study was prospective and prone to distortions such as selection bias due to loss of follow-up or patients' informed refusal. Since the method of infection diagnosis was based on clinical symptoms, patients with asymptomatic infections were possibly underdiagnosed. Another shortcoming in this study was not accounting for infections other than COVID-19 as confounding factors. Furthermore, the severity of infections was not assessed in our study. This study's larger sample size would have allowed us to conclude with narrower confidence intervals.

Conclusion

Our results can be considered preliminary evidence for the association of COVID-19 and higher overall EDSS scores and new MRI enhancements in RRMS patients. These findings highlight the increased risks of the recent pandemic for the MS patient population and underscore the importance of appropriate protective measures to prevent further deterioration of the patients' disease and quality of life. Nevertheless, additional studies are required for a more robust conclusion.

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Conflict of interest

None.

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