Research Article (Araştırma Makalesi)

Frequency of Covid-19 Infection and The Disease Profile in Patients Followed with Multiple Sclerosis

Multipl Skleroz Tanısı ile Takip Edilen Hastalarda Covid-19 Enfeksiyonu Geçirme Sıklığı ve Hastalık Profili

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Özet

Amaç: Multipl skleroz hastalığının (MS) ilerlemesini yavaşlatmak için uzun süredir immünomodülatör / immünsüpresif ilaçlar kullanılmaktadır. Bu tedavilerin bağışıklık sistemini baskıladığı ve enfeksiyonlara yatkınlık oluşturduğu bilinmektedir. Çalışmamızda mevcut koronavirüs (COVID-19) pandemisinde immünomodülatör/immünosupresif tedaviler alan MS hastalarının COVID-19 hastalık şiddeti ve sıklığının gözden geçirilmesi ve ayrıca psikolojik sonuçları açısından olumsuz etkilenip etkilenmediklerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Katılımcılar, nöroloji polikliniğinde takipli hastalık modifiye edici tedaviler (DMT) kullanan 18-65 yaş aralığında COVID-19 geçirmiş MS hastalarından (grup 1) ve benzer yaş ve cinsiyete sahip 2 farklı kontrol grubundan oluşmaktaydı. Diğer iki gruptan biri COVID-19 geçirmeyen MS hastaları (grup 2), diğeri ise COVID-19 geçiren ve MS olmayan hastalardan oluşuyordu (grup 3). Grup 1 ve 2 arasında MS profili, koronavirüs anksiyete ölçeği (CAS) ve Beck depresyon envanteri (BDI) ölçekleri; Grup 1 ve 3 arasında ise COVID-19 hastalık profili karşılaştırıldı.

Bulgular: 1. ve 2. grubun MS hastalık profili ile 1. ve 3. grubun COVID-19 hastalık profili açısından karşılaştırılması sonucunda bu ikili karşılaştırma gruplarında istatistiksel olarak anlamlı bir fark bulunamadı ($p > 0.05$) .

Sonuç: 2 MS grubu ve 2 COVID-19 geçiren grup karşılaştırıldığında istatistiksel olarak anlamlı bir fark görülmediği için DMT kullanımının MS hastalarında COVID-19 hastalık şiddetini artırmadığı ve COVID-19 geçirmenin MS hastalarının psikiyatrik durumlarında ekstra bir değişikliğe yol açmadığı sonucuna varılmıştır.

Anahtar kelimeler: COVID-19, Enfeksiyon, Hastalık modifiye edici tedavi, Multipl sklerosis

Abstract

Objective: For a long time immunomodulatory/immunosuppressive drugs have been used to slow the progression of multiple sclerosis (MS). These treatments are known to suppress the immune system and create susceptibility to infections. In our study, it was aimed to review the severity and frequency of COVID-19 disease in MS patients who received immunomodulatory/immunosuppressive treatments during the current coronavirus disease 2019 (COVID-19) pandemic, and also to evaluate whether they were adversely affected in terms of psychological outcomes.

Material and Methods: Participants consisted of MS patients who acquired COVID-19 (group 1) aged 18-65, using disease-modifying treatments (DMT) with follow-up in a neurology outpatient the clinic and the other two control groups consisted of similar ages and genders.

One of the other two groups is MS patients who have not had COVID-19 (group 2), the other group consisted of patients who had COVID-19 and did not have MS (group 3). MS profile, coronavirus anxiety scale (CAS), and Beck depression inventory (BDI) scales between groups 1 and 2; COVID-19 profile between groups 1 and 3 compared.

Results: As a result of comparing the MS disease profile of the 1st and 2nd groups and in terms of the COVID-19 disease profile of the 1st and 3rd groups, there was no statistically a significant difference in these paired comparison groups ($p > 0.05$).

Conclusions: It was concluded that DMT use does not increase the severity of COVID-19 and having COVID-19 does not cause any additional changes in the psychiatric status of MS patients, since no a statistically significant difference was observed in the 2 MS group and 2 COVID-19 group comparison.

Keywords: COVID-19, Disease-modifying treatment, Infection, Multiple sclerosis

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INTRODUCTION

Since MS is thought to have autoimmune/inflammatory etiopathogenesis in light of current knowledge, immunomodulatory/immunosuppressive treatments are used to modify the course of the disease. These treatments start with interferon group therapies, which have an immunomodulatory effect, and gradually evolve into treatments with more immunosuppressive effects (1). Since it is known that the immunosuppressive effects of new treatments are more pronounced, whether there is an increase in the risk of having an infectious disease in MS patients with these new treatments has become a current issue, and some specific infections due to some specific treatments have been reported (2). The best known of these is progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection reported with the use of natalizumab, fingolimod, and less commonly dimethyl fumarate and alemtuzumab (3). In addition, except for interferon and glatiramer acetate, it has been reported that there is an increase in both opportunistic and community-acquired infections due to MS treatments (4).

Therefore in this COVID-19 pandemic, COVID-19 catching rates and disease severity of MS patients using immunomodulatory/immunsuppressive therapy have been a matter of curiosity. Although it is predicted that the treatments used in MS will theoretically increase the rates of catching COVID-19 and the severity of the disease, some recent publications showed that these rates are not different from the normal population (5). In addition, some studies have suggested that some therapies used in the treatment of MS (fingolimod, beta interferon) may be useful even as adjuvants in the treatment of COVID-19 by balancing the exaggerated immune response (cytokine storming) that develops in COVID-19 infection or by showing antiviral activity (6).

In light of this information, we aimed to investigate the COVID-19 catching rates, severity of disease and psychological outcomes in MS patients followed up in our clinic, and to evaluate the relationship between these parameters and the MS profile of patients.

MATERIALS AND METHODS

3 groups of patients were included in our study. Patients caught COVID-19 infection among patients who followed up with MS in our clinic (group 1), an equal number of patients with MS who did not catch COVID-19 with similar age, gender, and EDSS score (group 2), an equal number of patients of similar age, gender from the non-MS population who caught COVID-19 (group 3) were included. RT-PCR test positivity was sought as an obligatory criterion for passing COVID-19 infection **(Table 1)**.

Table 1. Inclusion and exclusion criteria for groups

	Inclusion criteria	Exclusion criteria
Group 1	• Meeting the 2017 McDonalds (7) criteria for the diagnosis of MS • Being between the ages of 18-65 • Using DMT for MS • To agree to participate in the study and to give informed consent • Having had COVID-19 infection between March 12,2020 and September 30,2020	• Those who are suspected of having COVID-19 but PCR test is negative • Active COVID-19 symptoms during patient data collection process or continued hospitalization
Group 2	• Meeting the 2017 McDonalds (7) criteria for the diagnosis of MS • Being between the ages of 18-65 • Using DMT for MS • To agree to participate in the study and to give informed consent	• Having had COVID-19 infection between March 12,2020 and September 30,2020
Group 3	• To agree to participate in the study and to give informed consent • Having had COVID-19 infection between March 12,2020 and September 30,2020	• Those who are suspected of having COVID-19 but PCR test is negative • Active COVID-19 symptoms during patient data collection

MS: multiple sclerosis

DMT using MS patients in follow-up our clinic who have had COVID-19 (group 1) were identified by questioning the ID numbers of patients from the online case sample result query screen of the Public Health Management System between March and September 2020. MS profiles were obtained from patients' file tracking system and by phone call. For the MS profile; disease duration, last DMT and duration, MS clinical form, disability status (EDSS scoring was used), and ambulation status of MS were included. DMTs used by the patients were divided into 3 groups within the framework of expert opinions on whether or not they increase the risk of COVID-19. Interferons (IFN) and glatiramer acetate (GA) do not increase the risk; dimethyl fumarate (DMF), natalizumab (NTZ), and teriflunomide slightly increase the risk; fingolimod and ocrelizumab were classified as risk-increasing drug groups (8).

Information about COVID-19 disease characteristics and thoracic CT reports was obtained from the patient via telephone communication and the e-nabız system. Where the treatment is performed (home/hospital), whether there is a need for intensive care and/or invasive mechanical ventilation during hospitalization, the drugs used in the treatment, whether there is pneumonic involvement in CT, and which symptoms of COVID-19 experienced were questioned. The list of COVID-19 symptoms to be questioned was created according to the current COVID-19 symptom list (www.cdc.gov) determined by the American Center for Disease Prevention (CDC) (9).

In addition, to estimate mortality risk for groups 1 and 3, a modified COVID-19 mortality risk score (see **annex-1**), to assess post-COVID anxiety and depression for groups 1 and 2, coronavirus anxiety scale and Beck depression inventory was used.

The modified COVID-19 mortality risk score is a scoring system developed by Bello-Chavolla et al. and modified by Gabriel Bsteh et al., which aims to predict COVID-19 mortality based on scoring results. Scoring is done by questioning age, diabetes mellitus, chronic kidney disease, severe physical disability, smoking, cardiovascular disease, obesity, chronic obstructive pulmonary disease (COPD), and malignancy. According to the scoring results, it is categorized as low (≤0), mild (1-3), moderate (4-7), high (8-11), and very high risk (≥12) for COVID-19 mortality (10).

The coronavirus anxiety scale (CAS) developed by Lee et al. is a practical scoring system that aims to measure the anxiety level with short questions during this pandemic process. Consisting of 5 questions, each question aims to question the problem posed by a different anxiety form. Scoring between 0 and +4 is made in the answer of each question and the total score is calculated. A score of 9 and above accepts that anxiety is positive (11).

Annex-1. Modified COVID-19 mortality risk score

Factor	Score
Diabetes AND age <40 years	5
Age ≥65	3
Chronic kidney disease	3
Severe physical disability (EDSS >6)	2
Chronic obstructive pulmonary disease	1
Cardiovascular disease	1
Current malignancy	1
Obesity (BMI≥30)	1
Diabetes	1
Smoking	1
Age < 40	-6
Risk category	Score interval
Low risk	≤0
Mild risk	1-3
Moderate risk	4-7
High risk	8-11
Very high risk	≥12

BMI: body mass index. EDSS: expanded disability status scale.

The Beck Depression Inventory (BDI) was developed by Beck in 1961 and was revised in 1979 and 1996 is a scale that is still up-to-date in evaluating depression. It consists of 21 questions and each question has 0 to 3 points. Depression is suspected according to the total score of the test. Although the cut-off value for the presence of depression is generally accepted as 17 points, there is a classification of 10-16 points as mild depression, 17-29 points as moderate depression, and 30 points and above as severe depression (12). In a self-report study conducted to evaluate depression in MS, its sensitivity and specificity were found to be high for patients with MS (13).

Approval was obtained from İnönü University Clinical Research Ethics Committee for our study. Informed consent was obtained from all participants for the study via telephone communication.

Statistical Analysis

The data were given as median (min-max), mean ± standard deviation, and number (percentage). Conformity to normal distribution was made by the Shapiro-Wilk test.

Mann-Whitney U test, t-test, Pearson chi-square test, Yatesin corrected chi-square test, Fisher's exact chi-square test, and Spearman correlation coefficient were used for statistical analysis. A p value of <0.05 was considered statistically significant. IBM SPSS Statistics 25.0 program was used for analysis.

RESULTS

With the Public Health Management System query, among DMT using 629 MS patients, between March 10, 2020 and September 30, 2020 PCR test positive 29 patients who have had COVID-19 were identified. It was determined that 4.6% of our MS patients caught COVID-19 in a certain period. The demographic characteristics of the 3 groups are presented in **Table 2**. It is seen that all of the 3 groups show similar characteristics in terms of age, gender, and living place.

The MS characteristics of the two MS groups evaluated in the study (with and without COVID-19) are presented in **Table 3**. The age, gender and EDSS

Table 2. Demographic characteristics of groups and comparison

	Group 1	Group 2	Group 3
N	29	29	29
Mean age, years (SD)	35.70 ± 10.62	34.76 ± 8.80	35.00 ± 9.38
Gender			
Female	22(75.9%)	22(75.9%)	22(75.9%)
Male	7 (24.1%)	7 (24.1%)	7 (24.1%)
Living place			
Rural	2(6.8%)	2(6.8%)	2(6.8%)
City	27(93.1%)	27(93.1%)	27(93.1%)

Group 1: Patients with multiple sclerosis who have had COVID-19, Group 2: Patients with multiple sclerosis who have not had COVID-19, Group 3: Patients have had COVID-19 without multiple sclerosis

Table 3. General characteristics of group 1 and group 2

	Group 1	Group 2
MS duration/years (mean, SD)	7.14± 5.3	8.36± 6.4
Last DMT duration/months (mean, SD)	35.7± 31.3	33.6± 29.5
EDSS (mean, SD)	2.39± 1.63	2.37± 1.44
Last DMT		
Do not increase risk (IFN+GA)	4(13.7%)	6(20.6%)
Mildly risky (DMF, Teriflunomide, NTZ)	9(31%)	8(27.5%)
Risky (Fingolimod, Ocrelizumab)	16(55.3%)	15(51.7%)
MS clinical form		
RRMS	23(79.3%)	26(89.7%)
SPMS	6(20.7%)	3(10.3%)
Ambulation status		
Ambulatory	26(89.7%)	27(93.2%)
Ambulatory with asistance	3(10.3%)	2(6.8%)
CAS score mean, SD	1±2.8	1.17±2.6
BDI score mean, SD	14.3±9.0	15.4±10.4
Presence of anxiety according to CAS, n (percentage)	1(3.4%)	2(6.8%)
Depression level according to BDI scores, n (percentage)		
None	7(24.1%)	9(31.0%)
Mild	13(44.8%)	10(34.4%)
Moderate	5(17.2%)	4(13.8%)
Severe	4(13.8%)	6(20.6%)

Abbreviations: SD: standard deviation, IFN: interferons, DMF: dimethylfumarate, NTZ: natalizumab, RRSM: relapsing remitting ms, SPMS: secondary progressive ms, CAS: coronavirus anxiety scale, BDI: beck depression inventory.

characteristics of both groups appear to be similar. In this way, it was possible to compare the two groups in terms of disease duration, DMT used for MS and mean disease duration, MS clinical form, ambulation status, and psychological outcomes. There was no statistically significant difference between the two groups according to duration of MS, the last DMT used, duration of last DMT, ambulation status, MS clinical form, presence, and level of anxiety and depression according to CAS and BDI scores (p> 0.05).

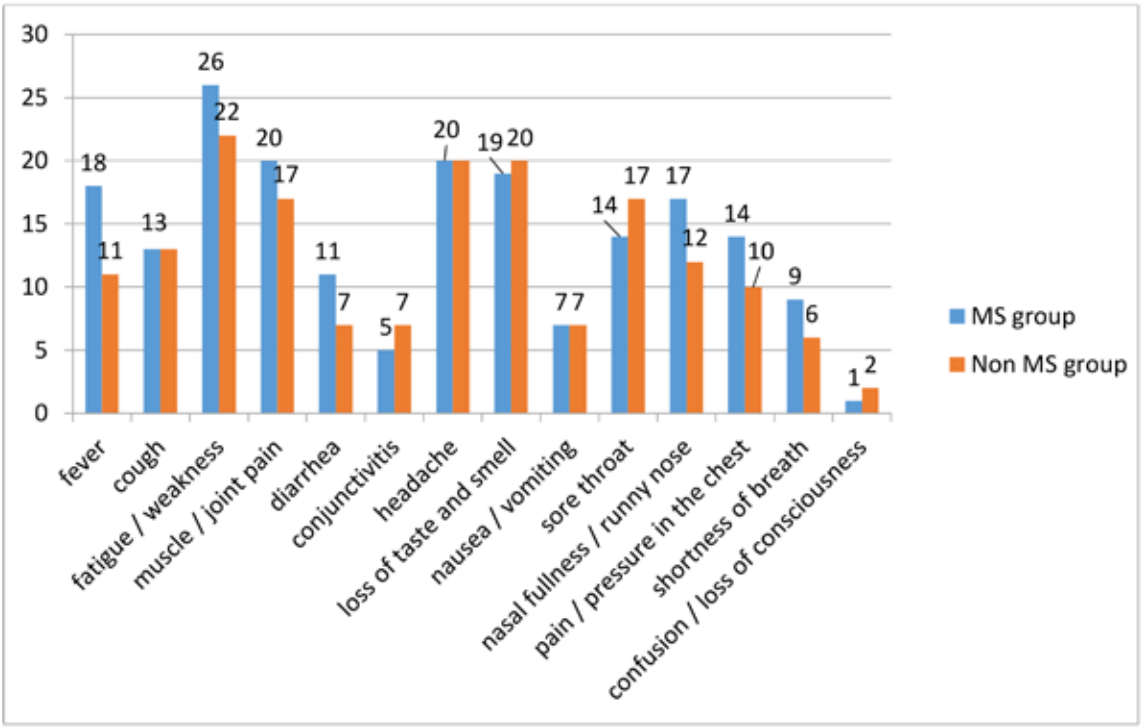
The average CAS score for the two groups is 1, 1.17, and the BDI mean score is 14.3, and 15.4, respectively. According to the BDI scores, the severity of depression is similar for the two groups. The two groups were compared in terms of the correlation between CAS and BDI scores, and there was no correlation between CAS and BDI scores (p> 0.05).

Groups 1 and 3 were compared in terms of COVID-19 characteristics (treatment location, thoracic CT involvement, treatments used). Treatment locations were the same for the two groups (96.6% at home, 3.4% at the hospital) Thoracic CT involvement rates were 24% (n:7) and 17% (n:5) for the two groups, respectively and no statistically significant difference was found (p> 0.05). COVID-19 treatment rates for hydroxychloroquine were 34.4% (n:10), %27,6 (n:8) for favipiravir 37.9% (n:11), 34.4% (n:10), hydroxychloroquine+favipiravir was 13.8% (n.4), 6.8% (n:2) respectively and again no statistically significant difference was found (p> 0.05). The rate of not using any COVID-19 treatment was lower in the MS group, with 13.8% (n = 4) and 31% (n = 9), respectively.

The symptom frequency and profile experienced by group 1 and group 3 with COVID-19 are shown in **Graphic 1**. The average number of symptoms experienced per person in the two groups was calculated as 6.6 and 5.8, respectively, and it was observed that both groups had the disease polysymptomatically. The most common symptom in both groups was fatigue/weakness and the least common symptom was confusion/altered consciousness. The symptom profile of the two groups was compared separately between the two groups, each as an independent variable, and there was no statistically significant difference (p> 0.05).

DISCUSSION

In our study, we aimed to investigate how the COVID-19 pandemic affects MS patients with the frequency, severity, and psychological consequences of the disease as it affects the whole society. Since it is known that DMT-using MS patients have a higher risk of infection than the non-MS population, in this COVID-19 pandemic, we compared MS patients with the other patients (group 3) selected from non-MS patients with similar characteristics to evaluate the difference in the rate of COVID-19, disease symptoms and severity compared to the non-MS population. In our



Graphic 1. Graphical comparison of the symptom profile of MS patients with COVID-19 and non-MS patients with COVID-19

clinic, among DMT-using MS patients we determined the rate of getting COVID-19 as 4.6% in a certain period (March 2020-September 2020). This rate was proportionally very high according to overall COVID-19 catching ratio data released by the Turkey Ministry of Health (4.6% to 0.38%) in the same time interval (14). However, as asymptomatic or mild cases are not included in the data of the Ministry of Health in these data, it is not very healthy to compare these two rates. When the MS group with COVID-19 and the non-MS group with COVID-19 were compared, no statistically significant difference was found between the symptom profile, thoracic CT involvement, and the treatments used. The most common symptom in both groups was weakness/fatigue. Since fatigue is also common in the basal state of MS patients, it is expected to be high in the MS group, but, surprisingly, it is similar in the non-MS patient group (15). In a similar study conducted by Parrotta et al. at New York University, the most common symptom in MS patients with COVID-19 was reported as fever and cough (16). In our study, no mortality was observed in the MS group with COVID-19, and only 1 (3.4%) patient was deemed necessary to be hospitalized, and the patient was discharged without the need for intensive care. In the study of Parotta et al., the rate of hospitalization was reported as 23.7% and mortality as 10.5%. In the same study, it was concluded that the use of DMT with MS does not increase the hospitalization frequency and mortality risk compared to the non-MS population. Similarly, in a multicenter Spanish study that reviewed the rates of COVID-19 and the severity of the disease in 5641 MS patients between February 2020 and May 2020, it was concluded that the frequency and severity of COVID-19 in MS patients were not higher than the normal population (17). In our study, the disease symptom frequency and pneumonia rates were not different from a population of similar age and gender and no mortality was observed in our MS patients with COVID-19 (in the light of available information, the average COVID-19 mortality was reported as 3% worldwide), It can be evaluated that the suppression of the cytokine storm with the use of DMTs, which hurts the prognosis of COVID-19 patients, balances the expected increase in disease severity in the MS group and even brings it to an advantageous position compared to the non-MS population (18-19).

In addition, in response to the question of what difference was there between MS patients who caught COVID-19 and those who did not. By comparing groups 1 and 2 in terms of MS duration, last DMT and duration, ambulation status, and MS clinical form the question of whether there is a difference between these two groups that facilitates the capture of COVID-19 was tried to be answered. There was no statistically significant difference was found in these parameters between the two groups. Fingolimod was the most commonly used drug in the MS group with COVID-19 with 13 patients. While the rate of fingolimod use in our total MS population was 31.3% (n: 201), this rate was 44% (n: 13) in the group with COVID-19. The rate of using fingolimod in the MS group without COVID-19 was 37.9% (n: 11).

Although there was no statistically significant difference between the two groups in terms of fingolimod use, the more frequent use of fingolimod in the group with COVID-19 and the reporting of severe cases of COVID-19 using fingolimod raise the question of whether fingolimod increases the risk of getting COVID-19 (20-21). However, a recent study that suggests that the immunomodulatory effect of fingolimod can be used experimentally to prevent progression to ARDS in critical patients with COVID-19 contradicts this interpretation (22).

Additionally, these two groups (group1-2) were compared using CAS and BDI scores in response to the question of whether COVID-19 exposure increases the frequency and severity of anxiety and depression in MS. There was no statistical difference between the two MS groups in terms of these scaling scores. Lee used CAS and reported anxiety rates above %30 among COVID-19 patients in March 2020, while this rate was 3.4% and 6.8%, respectively, in our two groups (23). The fact that these rates are lower in our study can be explained by the small size of our group samples and the possibility of living a longer time with the disease as a result of our evaluation of these scores for a long time than Lee (September 2020), causing this pandemic situation to normalize.

When the cut-off value for the presence of depression for BDI was accepted as 17 points, the depression rates in the two MS groups were found to be 31.0% and 34.4%, respectively. Since these rates are not different between the two groups and are compatible with the depression rates generally reported in MS patients, it can be interpreted that passing COVID-19 does not increase the frequency of depression in MS (24).

The limitations of our study were the inability to know the true number of asymptomatic or untested MS patients with COVID-19, our small sample size, and the inability to know the actual number of COVID-19 cases in the normal population in that date range. The low number of patients in the patient groups in our study made it difficult to compare the variables in these groups and to determine whether there was statistical significance between the groups. Similar studies in

larger MS populations will make it possible to make a better evaluation of the frequency and severity of COVID-19 in MS patients.

In conclusion, there are still many unknowns about the SARS-CoV-2 virus and the disease it causes. It has been a matter of curiosity how MS patients using DMT will be affected by the pandemic, like other patient groups using immunomodulatory and immunosuppressive drugs during the pandemic process. In general, most of the comorbid conditions (advanced age, diabetes, cardiovascular disease, chronic kidney and chronic lung disease, etc.) that increase the risk of COVID-19 mortality risk are not present in our MS community and because our MS patient population is relatively young, the predicted COVID-19 severity increase was not observed among our MS patients.

As the studies on this subject increase, it will be possible to better understand the course of COVID-19 in the MS population and similar immunomodulatory/immunosuppressive drug-using populations by clarifying the immunopathogenesis of the disease caused by the virus.

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Author Contribution: All authors contributed equally to the article

Ethical Approval: The ethics committee approval of the study was obtained from İnönü University Clinical Research Ethics Committee (Date: 07/10/2020; No:2020-151). Study procedures were performed likewise Helsinki Declaration. All participants signed a written informed form.

Informed Consent: An informed consent form was taken from the participants.

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