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Original article

## The course of COVID-19 infection in patients with multiple sclerosis–The experience of one center based on the population of Upper Silesia

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## ABSTRACT

**Background:** It is suspected that patients with multiple sclerosis (MS) are at greater risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection due to disability and immunotherapy. The relationship between MS and coronavirus disease 2019 (COVID-19) is uncertain. The aim of the study was to collect and analyze this relationship.

**Methods:** All MS patients of the Neurological Outpatient Clinic in Zabrze, Poland, were regularly questioned for the symptoms of COVID-19 and contact with an infected person. Patients that presented with COVID-19 symptoms or confirmed contact with an infected person were referred for the COVID-19 test. All patients with confirmed SARS-CoV-2 infection ( $n = 41$ ) were included in the analysis. Medical records of the study group were analyzed. Patient condition was monitored in the outpatient clinic after recovery. In 26 subjects, additional examinations, including brain magnetic resonance imaging (MRI), electroneurography (ENG), electroencephalography (EEG), color duplex Doppler (CDD), visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs) and psychological assessment were performed following recovery.

**Results:** Only one patient required hospitalization during COVID-19 infection, whereas 87.80% of patients did not require treatment for COVID-19. In all patients, C-reactive protein (CRP) levels were below 10 mg/L. In 2.44% of patients, oxygen partial pressure was below 95%. In most MS patients, the results of further examinations after COVID-19 infection were similar to those prior to infection. Psychological assessment revealed that anxiety was found in 42.31% of patients.

**Conclusions:** A mild course of COVID-19 in MS patients seems common despite disease-modifying drug treatment and disability. Self-isolation is recommended to reduce the number of infected patients. COVID-19 infection did not worsen the course of MS in most subjects. Patients with MS may require additional psychological support during the pandemic due to their susceptibility to anxiety.

### 1. Introduction

The outbreak of the novel coronavirus disease 2019 (COVID-19) pandemic has become a serious challenge to many areas of medicine, including neurology. Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present with a variety of symptoms, including anosmia, ageusia, headache, or dizziness. The disease may also lead to neurological complications, i.e., stroke, epileptic seizures, or Guillain-Barre syndrome (GBS). It has been proven that SARS-CoV-2 has tropism to the nervous system (Adamczyk-Sowa et al., 2020a). Since COVID-19 was a novel disease, no recommendations or treatment strategies for chronic neurological diseases were available at

the onset of the pandemic. Management of multiple sclerosis (MS) during the COVID-19 pandemic is of special concern since MS is a chronic demyelinating disease leading to irreversible injury to the brain and spinal cord. At the onset of the pandemic, it was suspected that patients with MS were at greater risk for SARS-CoV-2 infection due to disability and immunotherapy. According to Mohn et al., better outcomes were reported for patients treated with disease-modifying therapies. It seems that MS therapy could be protective of COVID-19. It may also appear that patients who are not on immunomodulatory therapy are more likely to present with an advanced stage of the disease (Möhn et al., 2020). The risk of infection differs in patients and can be increased by comorbidities and older age (Hamdy et al., 2020).

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Infectious diseases may also lead to the deterioration of MS. The relationship between MS and COVID-19 is uncertain. However, the first European observations from Italy (where the effects of the pandemic were particularly visible) showed that the severity of COVID-19 infection in most patients was mild (Sormani, 2020).

Upper Silesia is a territory of Poland with the largest population per square kilometer (376 persons per km<sup>2</sup>) (Data from 31.10.2010 based on Local Data Bank, Central Statistical Office (in Poland)) The number of patients infected with COVID-19 in this region was the highest in Poland for a long time. As a result, self-isolation was recommended for patients. Another challenge was to organize the access of MS patients to health-care. Many consultations were delivered via telemedicine. Great efforts were required to monitor the condition of patients and select those with relapse or at risk of COVID-19 infection.

The aim of the study was to collect and analyze data related to the relationship between MS and COVID-19.

**2. Materials and methods**

In 2020, the condition of MS patients was monitored in the Neurological Outpatient Clinic in Zabrze, Poland, and via telemedicine. All MS patients of the outpatient clinic were regularly questioned for symptoms of COVID-19 and contact with an infected person. Patients that presented with COVID-19 symptoms or confirmed contact with an infected person were referred for the COVID-19 test. All patients with confirmed SARS-CoV-2 infection (n = 41) were enrolled in the study. The inclusion criteria were as follows: age ≥18, diagnosis of MS according to the McDonald Criteria (2005, 2010, 2017), COVID-19 infection confirmed by positive RT-PCR nasopharyngeal swab or a positive immunological test. This analysis was based on a review of the medical history of patients.

The second part of the study was conducted after recovery. The aim of this assessment was to check the impact of SARS-CoV-2 infection on the course of MS. The condition of patients was monitored in the outpatient clinic and the subjects were encouraged to participate in further examinations. Participation in the study was voluntary and 26 patients who gave written informed consent were enrolled in the second part of the study.

A total of 41 patients were enrolled in the study. All patients were treated in our referral center. Female patients were predominant (73.17%; mean age 40.88±11.88 years). The baseline characteristics of the study participants are given in Table 1. MS treatment before the infection is given in Table 2. Medical records of the study group were screened for comorbidities (Table 3).

**3. Statistical analysis**

The continuous variables were shown as mean and standard deviation (SD) or median values and an interquartile range (IQR), when appropriate. The categorical variables were presented as the percentage.

**Table 1**  
Baseline characteristics of the study participants.

Number of participants	41
EDSS	3.50 [3.00–4.00]
Type of MS	
RRMS [%]	92.68
PPMS [%]	7.32
MS duration [years]	4.00 [2.00–9.00]
Relapse in the last 3 months [%]	9.76
Steroid therapy in patients with relapse (n = 3) [%]	100
Duration of MS therapy before COVID-19 infection [years]	3.00 [1.50–8.50]
Discontinuation of DMD during COVID-19 infection n = 28 [%]	2.50

DMD – disease-modifying drug, EDSS - Expanded Disability Status Scale, PPMS - primary progressive multiple sclerosis, RRMS - relapsing-remitting multiple sclerosis,.

**Table 2**  
MS treatment prior to COVID-19 infection.

MS treatment	Percentage of patients
Interferon	17.07
Glatiramer	7.32
Teriflunomide	7.32
Dimethyl fumarate	43.90
Natalizumab	2.44
Ocrelizumab	7.32
Mitoxantrone	2.44
Other	7.32
None	4.88

**Table 3**  
Comorbidities in MS patients.

Comorbidities	Percentage of patients
Arterial hypertension	12.20
Diabetes	4.88
Coronary artery disease	4.88
Asthma	4.88
COPD	0
Liver disease	2.44
Kidney disease	0
Immune deficiencies	0
Neoplastic diseases	0
Hypothyroidism	12.20
Dyslipidemia	12.20
Smoking	4.88
Other	0
None	65.85

COPD - chronic obstructive pulmonary disease.

All statistical analyses were performed using Statistica 13.1.

**4. Results**

The diagnosis of COVID-19 was confirmed by a positive RT-PCR test (78.05%) or a positive immunological test (21.95%). Most patients (97.56%) had contacted an infected person prior to infection. The mean number of COVID-19 symptoms in MS patients was 4.32±2.03. The first symptoms of COVID-19 in MS patients are given in Table 4. Only one patient from the study group required hospitalization during COVID-19 infection. Other patients were isolated at home. Chest computed tomography (CT), which was performed in 7.32% of patients, showed the symptoms of interstitial pneumonia in 33.33% of subjects. Other patients had no abnormalities on CT. Treatment of COVID-19 was not required in 87.80% of patients. Treatment with glatiramer was

**Table 4**  
The first symptoms of COVID-19 in MS patients.

Symptoms of COVID-19	Percentage of patients
Fever	56.10
Dry cough	48.78
Fatigue	34.15
Sore throat	7.32
Headache	46.34
Muscle pain	31.71
Bone and joint pain	36.59
Swelling of the nasal mucosa	4.88
Chills	7.32
Dyspnea	19.51
Rash	2.44
Anosmia	65.85
Ageusia	60.98
Pneumonia	2.44
Diarrhea	4.88
Vomiting	0
Abdominal pain	0
None	0

discontinued in only one patient during SARS-CoV-2 infection. Blood tests in patients with COVID-19 showed that WBC was below  $3 \times 10^3/\text{mm}^3$  in only 4.88% of patients and the lymphocyte count was below  $1 \times 10^3/\text{mm}^3$  in 14.63% of subjects. C-reactive protein (CRP) levels above 10 mg/L were found in none of the patients. Oxygen partial pressure below 95% was reported in 2.44% of patients. The symptoms of COVID-19 were present for at least two weeks after recovery in 56.41% of patients. The patients' condition was monitored in the outpatient clinic following recovery and they were encouraged to participate in further examinations (Table 5). Psychological assessment was conducted in 26 (63.41%) patients. Anxiety and fear were found in 42.31% of the study group. Cognitive functions were within normal limits in all patients.

## 5. Discussion

Our department is a referral center for many patients with MS. The group of patients diagnosed with SARS-CoV-2 infection seemed small, which may have been related to self-isolation. However, the number of patients with asymptomatic SARS-CoV-2 infection was unknown. Mantero et al. found that the prevalence of COVID-19 in MS patients was not different than that in the general population (Mantero et al., 2020).

As patients on disease-modifying drugs (DMDs) are at greater risk of infection, further treatment during the pandemic was under discussion among experts. Approved disease-modifying therapies were continued because prevention of further progression of MS outweighed the risk of COVID-19 infection (Zrzavy et al., 2020). Expert recommendations related to COVID-19 were inconclusive. Hamdy et al. suggested that DMD therapy should be discontinued in patients with active COVID-19 infection. (Hamdy et al., 2020) The Section of MS and Neuroimmunology of the Polish Neurological Society recommend discussing this issue with patients and consider their age, clinical condition and the type of DMD (Bartosik-Psujek et al., 2020). Therapy should be continued in the case of a mild course of the infection or during treatment with interferon, glatiramer, teriflunomide, dimethyl fumarate and in patients without lymphopenia ( $<800/\text{ul}$ ).<sup>8</sup> It was recommended that discontinuation of DMD should be considered in the case of immunosuppressive therapy, in patients older than 60 years of age, in those with concomitant diseases and with moderate to severe course of infection (Bartosik-Psujek et al., 2020). A study of Sormani et al. found that the severity of COVID-19 infection was mild in 96% of MS patients. (Sormani, 2020) In our study group, the course of SARS-CoV-2 infection was mild despite DMD treatment. Discontinuation of therapy was not required in our patients. However, treatment was discontinued in one subject. In MS patients who were treated with DMD, the mortality rate during COVID-19 infection was 4% (Möhn et al., 2020). According to Laroni et al., DMD treatment may decrease inflammation, thus leading to milder forms of COVID-19. However, they indicated that innate immune system was particularly responsible for dysregulated inflammatory response to COVID-19 and the impact of DMD on this response was limited (Laroni et al., 2020). It seems that DMD treatment, previous cardiovascular disease or a severe degree of disability were not adverse prognostic factors for MS patients (Möhn et al., 2020).

Increased CRP levels and depletion of CD4 and CD8 lymphocytes

**Table 5**  
Further examinations following recovery from COVID-19.

Examination	Deterioration after infection or abnormal results
Brain MRI $n = 26$ [%]	3.85
VEP $n = 25$ [%]	4.00
BAEP $n = 24$ [%]	0
ENG $n = 24$ [%]	0
EEG $n = 24$ [%]	0
CDD $n = 25$ [%]	0

BAEP- brainstem auditory evoked potential, CDD - color duplex Doppler, EEG - electroencephalography, ENG - electroneurography, MRI - magnetic resonance imaging, VEP - visual evoked potential.

with associated lymphopenia were observed in patients during COVID-19 infection (Adamczyk-Sowa et al., 2020b). However, laboratory findings were within normal ranges in most patients in our study. No clear relationship was observed between low lymphocyte count and disease severity in MS patients (Loonstra et al., 2020).

SARS-CoV-2 can infect neurons and glial cells using angiotensin-converting enzyme 2 (ACE2) receptors (Adamczyk-Sowa et al., 2020a). Neurological manifestations of COVID-19 such as anosmia, ageusia, epileptic seizures or an increased risk of stroke were confirmed (Adamczyk-Sowa et al., 2020a). More than 36% of patients hospitalized due to COVID-19 infection presented with neurological symptoms (Adamczyk-Sowa et al., 2020b). Anosmia, ageusia and fever were the most prevalent complaints among MS patients. The association between the presence of COVID-19 symptoms and increased relapse rates has not been demonstrated. However, systemic infections are associated with an increased risk of MS relapse (Segamarchi et al., 2020). COVID-19 infection was not related to the worsening of MS in most patients. Deterioration of the clinical condition in MS patients may be observed during infection or fever. Such deterioration does not have to be associated with the occurrence of new lesions, as it may be a pseudo relapse. In most MS patients, the results of magnetic resonance imaging (MRI), visual evoked potentials (VEPs), and brainstem auditory evoked potentials (BAEPs) after the infection were similar to those prior to infection. In patients with COVID-19, *de novo* seizures were reported (Asadi-Pooya et al., 2020). Electroencephalography (EEG) findings of patients with SARS-CoV-2 infection showed sporadic epileptiform activity (mostly frontal sharp waves) and generalized background slowing, particularly in patients with a decreased level of consciousness (Sharifian-Dorche et al., 2020). No abnormalities during the EEG recording were found. Electroneurography (ENG) in patients with COVID-19 infection was performed in subjects with Guillain-Barre syndrome (GBS) and revealed only the characteristic features typical of GBS (i.e., acute demyelinating polyneuropathy and axonal polyneuropathy) (Adamczyk-Sowa et al., 2020a). Manganotti et al. described subclinical involvement of the facial nerve detected by ENG in patients with ageusia who underwent examination to detect GBS and polyneuritis cranialis (Manganotti et al., 2021). To the best of our knowledge, ENG findings in patients after SARS-CoV-2 infection without GBS have not been reported yet. In our study group, the results of ENG were normal. COVID-19 infection may result in vascular complications, especially stroke (Pezzini and Padovani, 2020). Therefore, color duplex Doppler (CDD) was used in the study. However, CDD showed no abnormalities.

The neuropsychiatric effect of the pandemic was analyzed. Among the medical personnel in China, anxiety and stress disorder were found in 23% and 27% of individuals, respectively (Haji Akhondi et al., 2020). Patients seem to be more susceptible to the neuropsychiatric impact of the COVID-19 pandemic (Haji Akhondi et al., 2020). Anxiety, depression, fatigue and cognitive disorders are reported in this group of patients even in the early stages of the disease. The prevalence of anxiety before the COVID-19 pandemic outbreak was estimated at 22.1% in MS patients. However, it varied significantly across studies (Boeschoten et al., 2017). COVID-19 infection seems to be linked to an increase in anxiety. Vogel et al. reported that most patients with MS reported interruptions to their MS care and limited access to COVID-19 testing, which may have been the cause of this increase (Vogel et al., 2020). Woo et al. reported that patients after COVID-19 recovery presented with substantial neurocognitive deficits related to attention, short-term memory and concentration and language tasks (Woo et al., 2020). However, their cognitive status remained unchanged.

## 6. Conclusions

A mild course of COVID-19 seems common despite DMD treatment and disability. Self-isolation is recommended to reduce the number of infected patients. In our study, COVID-19 infection did not worsen the course of MS in most patients. Additional psychological support should

be provided to MS patients during the pandemic due to their susceptibility to anxiety.

## 7. Limitations of the study

Due to the small number of patients enrolled in the study, the results should only be regarded as preliminary. Further studies are warranted to analyze the relationship between COVID-19 and MS.

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## Declaration of Competing Interest

There was no conflict of interest.

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