Title

Assessing the susceptibility to acute respiratory illness COVID-19-related in a cohort of multiple sclerosis patients

Permalink

https://escholarship.org/uc/item/80t6p3z1

Authors

Mantero, Vittorio
Abate, Lucia
Balgera, Roberto
et al.

Publication Date

2020-11-01

DOI

10.1016/j.msard.2020.102453

Peer reviewed

Original article

Assessing the susceptibility to acute respiratory illness COVID-19-related in a cohort of multiple sclerosis patients

Vittorio Mantero[a,*], Lucia Abate[b], Roberto Balgera[a], Paola Basilico[a], Andrea Salmaggi[a], Christian Cordano[c]

[a] *MS Center, Department of Neurology, ASST Lecco, Lecco, Italy*
[b] *MS Center, Department of Neurology, ASST Lariana, Como, Italy*
[c] *UCSF Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA*

ARTICLE INFO

ABSTRACT

Introduction: Italy has been the first European country severely affected by the COVID-19 pandemic.
Objective: To analyze the incidence of the clinical presentations suggestive for COVID-19 infection among patients with Multiple Sclerosis in the province of Lecco, in the North Italy, the closest province capital to Bergamo. To describe the association of demographics, clinical characteristics, and use of DMTs categories with the risk of contracting the disease.
Methods: We telephonically interviewed all the 275 MS patients followed in the MS center. The collected data included recent contact with a patient with COVID-19 diagnosis or a subject with respiratory symptoms and the developing of COVID-19 symptoms or a confirmed diagnosis.
Results: 15 out of 275 patients reported symptoms suggestive for COVID-19 infection, only one of them with PCR-confirmed diagnosis. No one of them presented severe symptoms or needed hospitalization. Using a multivariable logistic regression model, the only factor associated with being in the COVID-suspect group was the report of a recent contact with a patient with a COVID-19 diagnosis.
Conclusions: The prevalence of COVID-19 within MS patients seems to resemble the prevalence in general population. The lack of associations with other factors assessed, including DMTs, may reflect a lack of statistical power. Larger population studies are needed to explore the correlation between different disease-modifying therapies and COVID-19 course.

1. Introduction

The coronavirus disease 2019 (COVID-19) infection has been shown to be more severe in patients with comorbidities, such as diabetes, cardiovascular disease and general organ and coagulation dysfunction (Mehra et al, 2020; Wu et al, 2020). The risk and course of COVID-19 in patients with multiple sclerosis (MS), however, is unclear. Although neurological disability and underlying immune alterations may be important, the common use of immune-based disease modifying therapies (DMTs) in patients with MS has attracted the most attention in this regard (Sormani, 2020; Mantero et al, 2020). A recent paper reported on 86 patients with immune-mediated inflammatory diseases and confirmed or suspected Covid-19 (Haberman et al, 2020). It showed an incidence of hospitalization similar to Covid-19 patients in the general population in New York City. The use of biological immunomodulators did not seem to be associated with a worse prognosis. However, that

study did not report on patients with MS or MS-specific DMTs. Sormani et al. recently reported on 232 patients with MS (57 of whom tested positive for COVID-19 and 175 of whom had suspected COVID-19 symptoms) from 38 different MS center (Sormani, 2020). 223 patients presented with mild symptoms, 4 with severe infection; 6 were considered critical and 5 of them died. The Italian Study Group For COVID-19 will continue gathering more patients' data, including data from our work, throughout the duration of the pandemic, with the goal to inform about any susceptibility to protection from COVID-19 afforded by disease-modifying therapies.

Italy was the first European country severely affected by the COVID-19 pandemic, while Bergamo represented the epicenter of the Italian COVID-19 infection (Fagiuoli et al. 2020).

Here, we describe a cross-sectional study performed in Lecco, the closest province capital to Bergamo, to analyze the incidence of the clinical presentations suggestive for COVID-19 infection among patients

---

Fig. 1. Map of Lombardy, with the province of Lecco highlighted.

with MS and describe the association of demographics, clinical characteristics, and use of DMTs with the risk of developing COVID-19.

Lecco is a province with a population of approximately 340.000 inhabitants, situated in Lombardy, in close proximity to Lake Como and in the neighboring mountain area. As of May 11, 2.537 patients received a diagnosis of COVID-19 infection. A map is represented in Fig. 1.

2. Methods

This is a cross-sectional study of patients with MS who are managed by two neurologists in the Multiple Sclerosis Center of Lecco (VM and RB). We interviewed all the patients followed in the MS center from May 2 to May 6, 2020 via telephone. Collected data included recent contact with a patient with COVID-19 diagnosis or a subject with respiratory symptoms, whether they have developed any of these symptoms after February 23, 2020: fever, cough, shortness of breath, sore throat, sneezing and runny nose, ageusia, anosmia, nausea or vomiting and diarrhea, whether and how they have been diagnosed with COVID-19 by a healthcare professional and if so, their disposition (home, hospital ward or an ICU). Age, sex, type of MS (determined by clinical records), current DMT, day of the last dose of treatment, the length of being on the current DMT and disability level (EDSS) were collected from the MS Center database. We defined a COVID-19-suspect group as patients who had at least 2 of the following symptoms: fever, cough, shortness of breath, anosmia, or ageusia.

Analyses were performed using Stata 14.1 (StataCorp, TX). Significant differences in the demographic, clinical characteristics, between COVID-19-suspect cases and the rest of the respondents were tested using Fisher's exact test for categorical variables and Kruskal–Wallis tests for continuous variables. We categorized the DMTs based on their mechanisms of action into three groups: Immune cell depleting medications (alemtuzumab, ocrelizumab and cladribine), immune-cell trafficking inhibitors (fingolimod and natalizumab), other DMTs (including glatiramer acetate, interferons, dimethyl fumarate (DMF), teriflunomide, mycophnolate mofetil and azathioprine) and no-

DMT group. To determine if any DMT category was independently associated with the COVID-19-suspect status, we used a multivariable logistic regression model with COVID-19-suspect status as the outcome, DMT categories (categorized as immune cell depleting medications, immune-cell trafficking inhibitors, other DMTs, and no DMT) as the predictor, and adjusted for the following covariates: age, sex, MS type, disease duration, EDSS, report of a recent contact a patient with COVID-19 diagnosis, and the report of a recent contact a patient with respiratory symptoms.

3. Results

A total of 275 patients, all the patients followed in the MS center, participate in the study (responded to the phone questionnaire). The majority of patients (79.3%) resided in the province of Lecco, while 55 (20%) in the neighboring provinces of Como, Monza, Bergamo and Sondrio and 2 patients (0.7%) in the province of Milan. The patients were mostly female (65.8%) with a mean (SD) age of 46.4 (13.2) years. 5.5% had a clinically isolated syndrome (CIS), 83.3% had relapsing-remitting (RRMS), and 7.6% had secondary progressive MS (SPMS), 3.6% primary progressive MS (PPMS). The average disease duration was 11.8 ± 9.3 years.

82.5% of the respondents were on active treatment with one of the DMTs for MS as follows: interferons 20%, DMF 18.9%, glatiramer acetate 11.3%, teriflunomide 9.5%, fingolimod 7.6%, natalizumab 7.3%, alemtuzumab 1.8%, ocrelizumab 1.8%, mycophenolate mofetil 1.1% and cladribine 0.7%. The last dose of alemtuzumab were administered for over a year in all patients, cladribine for more than 4 months, while ocrelizumab were administered between January and February in all the four patients.

The median EDSS was 1.5 (IQR 1-4). Out of 275 patients, 1 (0.3%) was diagnosed with COVID-19 after PCR execution. Other 14 (5.1%) patients fulfilled our criteria for the COVID-19-suspect group, as described in the methods.

Fifteen patients were categorized as COVID-suspect (5.5% of the responders): fourteen patients were qualified by their reported symptoms and one patient reported a positive PCR test. Fourteen out of 15 patients were recommended to stay home and monitor the symptoms. They all improved without receiving any specific treatment. One was treated with levofloxacin for one week and eventually improved. One of the patients reported left hand paresthesia during the respiratory symptoms, interpreted as a pseudo-relapse by the neurologist.

No patient required hospitalization, ICU care or intubation.

The demographic and clinical characteristics of COVID-19-suspect and non-suspect patients are summarized in Table 1.

Age, sex and MS type of COVID-suspect group were not different from the rest of survey responders. No patient in the COVID-suspect group was on therapy with immune cell depleting medications, 2 (13.3%) were treated with immune-cell trafficking inhibitors (1 fingolimod and 1 natalizumab), 12 (80%) were in therapy with other DMTs (7 DMF, 3 interferons and 2 teriflunomide) and 1 (6.7%) received no DMTs. There was no statistically significant difference in the proportion of patients on different DMT categories between the two groups (Fisher's exact test p-value = 0.58): 5% of patients in the rest of participants (the none-COVID-19-suspect group) were on B-cell depleting medications, 15% on immune-cell trafficking inhibitors, 61% on other DMTs and 19% were not on therapy.

The proportion of patients in the non-COVID-19-suspect group who reported a recent COVID-19 case contact was only 6.9% (p-value < 0.001). In multivariable logistic regression model (Table 2), the only factor associated with being in the COVID-suspect group was the report of a recent contact with a patient with a COVID-19 diagnosis: 53.3% of patients in the COVID-19-suspect group reported a recent contact with a diagnosed COVID-19 case.

Table 1

Comparison of demographic, clinical and DMTs data between suspected COVID-19 MS patients and non-COVID MS patients

	COVID-suspect patients N = 15	The rest of survey respondents N = 260	*p*-value*
Female, n (%)	10 (67%)	171 (66%)	**1.00**
Age mean (SD), y	40.5 (13.7)	46.7 (13.1)	**0.11**
MS type, n (%)			**1.00**
CIS	0	15 (6%)	
Relapsing	14 (93%)	215 (83%)	
Progressive	1 (7%)	30 (11%)	
Disease duration mean (SD), y	11.5(9.2)	11.9 (9.4)	**0.92**
DMT category, n (%)			**0.58**
Immune cell depleting medications	0	12 (5%)	
Immune-cell trafficking inhibitors	2 (13%)	39 (15%)	
All other DMTs	12 (80%)	159 (61%)	
No DMT	1(7%)	50 (19%)	
EDSS median (IQR)	2.0 (1.5, 3.0)	1.5 (1.0, 4.0)	**0.51**
Was in contact with a diagnosed COVID-19 case, n (%)	8 (53%)	11 (4%)	**<0.001**
Was in contact with a person with a patient with respiratory symptoms, n (%)	5 (33%)	12 (5%)	**0.001**

• Fisher's exact test or Kruskal-Wallis test

MS: multiple sclerosis, CIS: clinically isolated syndrome, EDDS: Expanded Disability Status Scale, Immune cell depleting medications included ocrelizumab, alemtuzumab and cladribine; Cell trafficking inhibitors included fingolimod and natalizumab; Other DMTs group included glatiramer acetate, interferons, dimethyl fumarate, teriflunomide, mycophnolate mofetil, azathioprine.

Table 2

Risk factors of COVID-19 infection in MS patients

	Odds ratio	95% CI	*p*-value
Female (compared to male)	1.03	0.26, 4.12	0.96
Age (one year increase)	0.92	0.84, 1.01	0.083
Disease duration (one year increase)	1.06	0.96, 1.17	0.23
MS type (progressive compared to relapsing)	1.26	0.05, 30.28	0.89
DMT category (compared to No-DMTgroup)			0.62
Immune cell depleting medications	1	0.13, 59.25	
Cell trafficking inhibitors	2.82	0.24, 63.32	
Other DMTs	3.90		
EDSS (one step increase)	1.39	0.82, 2.36	0.23
Report of a recent contact with a patient with COVID-19 diagnosis	27.29	6.28, 118.66	<0.001
Report of a recent contact with a person with respiratory symptoms	4.42	0.78, 26.96	0.093

MS: multiple sclerosis, EDDS: Expanded Disability Status Scale, DMT: disease-modifying treatment. Immune cell depleting medications included ocrelizumab, alemtuzumab and cladribine; Cell trafficking inhibitors included fingolimod and natalizumab; Other DMTs group included glatiramer acetate, interferons, dimethyl fumarate, teriflunomide, mycophnolate mofetil, azathioprine.

4. Discussion

More than 5% of the patients with MS surveyed in this study reported symptoms suggestive for COVID-19 infection. We did not find an association between the demographics and clinical characteristics and the odds of being in the COVID-suspect group.

As of May 11, 2020, the Lecco province had 2536 confirmed cases with 12% of deaths from COVID-19, although estimates are over 20,000 infected. Sixty hundred twelve patients had been hospitalized and 98

required ICU. Considering the population of Lecco's province, (337,380 in 2019) (Italian National Institute of Statistics, ISTAT, 2019), the prevalence of confirmed cases is 0.8%, while the estimates infected can be roughly quantified around the 6% of the population.

In our cohort, the incidence of clinical presentations suggestive for COVID-19 infection (5.4%) and the incidence of confirmed cases among MS patients (0.3%) does not seem to differ meaningfully from the general population. Interestingly, no patients needed hospitalization or advanced treatments.

Our study was not designed to establish the incidence of COVID-19 among MS patients. However, even if MS patients are generally twice as likely to be hospitalized for infections than the general population, (Wijnands et al., 2017) our results suggest that in our cohort this was not true for the COVID-19 infection. This finding can be due to either an extremely cautious behavior from the perception of being a "population at risk", and to the demographics of our cohort (low disability and young age).

In our cohort there were very few patients on immune-cell depleting medications (ocrelizumab, alemtuzumab, and cladribine). This characteristic of the cohort did not allow us to investigate the possibly harmful effects of cell-depleting therapies on COVID-19 infection, recently described by Safavi et al. (2020).

We also did not find an association between the demographic characteristics, MS disease duration and disability levels with the risk of being in the COVID group. As the number of participants in the COVID-suspect group was small, these results should be interpreted with caution. Indeed, the lack of association of severity with DMT can be due to a too small sample size.

This study allows for a preliminary overview of the consequences of the COVID-19 infection in patients with MS in the first few weeks of the epidemic in Northern Italy. The sample size was not large, but we were able to interview all the patients followed by the MS Center of the province and we used a multivariable model for finding independent risk factors. The study has some limitations. We alluded to the limited sample size, and to biases that could have led to the observations of a higher proportion of disease-suspect patients and a more benign course in our study. Only one of our patients was tested with the gold standard testing for the diagnosis of COVID-19 (the PCR of the nasopharyngeal swab).

5. Conclusions

In conclusion, our results showed that MS patients developed symptoms suggestive for COVID-19 in the province of Lecco with a prevalence very similar to the general population. No patient required intensive care or intubation. The lack of association we found can be indeed due to the impossibility to detect an association, due to a too small sample size. Therefore, the effect of different DMTs on the susceptibility to the COVID-19 infection needs to be evaluated with larger studies reporting databases (registries), currently collecting data to better understand the risk of COVID-19 infection and its course in patients with MS.

CRediT authorship contribution statement

Vittorio Mantero: Conceptualization, Methodology, Writing - original draft, Visualization. **Lucia Abate:** Investigation, Writing - review & editing. **Roberto Balgera:** Investigation, Writing - review & editing. **Paola Basilico:** Investigation, Writing - review & editing. **Andrea Salmaggi:** Writing - review & editing, Supervision. **Christian Cordano:** Conceptualization, Formal analysis, Visualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Fagiuoli, S, Lorini, FL, Remuzzi, G, 2020. Covid-19 Bergamo Hospital Crisis Unit. Adaptations and lessons in the Province of Bergamo. N. Engl. J. Med. https://doi.org/10.1056/NEJMc2011599.

Haberman, R, Axelrad, J, Chen, A, Castillo, R, Yan, D, Izmirly, P, Neimann, A, Adhikari, S, Hudesman, D, Scher, JU, 2020. COVID-19 in immune-mediated inflammatory diseases - case series from New York. N. Engl. J. Med. https://doi.org/10.1056/NEJMc2009567.

Italian national institute of statistics, ISTAT2019. http://demo.istat.it/bilmens2019gen/index02.html.

Mantero, V, Abate, L, Basilico, P, Balgera, R, Salmaggi, A, Nourbakhsh, B, Cordano, C, 2020. COVID-19 in dimethyl fumarate-treated patients with multiple sclerosis. J. Neurol. https://doi.org/10.1007/s00415-020-10015-1.

Mehra, MR, Desai, SS, Kuy, S, Henry, TD, Patel, AN, 2020. Cardiovascular disease, drug therapy, and mortality in COVID-19. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa2007621.

Safavi, F, Nourbakhsh, B, Azimi, AR, 2020. B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with Multiple Sclerosis during the early COVID-19 epidemic in Iran. Mult. Scler. Relat. Disord. https://doi.org/10.1016/j.msard.2020.102180.

Sormani, MP, 2020. Italian Study Group on COVID-19 infection in multiple sclerosis. An Italian programme for COVID-19 infection in multiple sclerosis. Lancet Neurol 2020 Apr 30. pii: S1474-4422(20)30147-2.

Wijnands, JM, Kingwell, E, Zhu, F, Zhao, Y, Fisk, JD, Evans, C, Marrie, RA, Tremlett, H, 2017. Infection-related health care utilization among people with and without multiple sclerosis. Mult. Scler. 23 (11), 1506–1516.

Wu, C, Chen, X, Cai, Y, Xia, J, Zhou, X, Xu, S, et al., 2020. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 Pneumonia in Wuhan, China. JAMA Intern. Med.