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Commentary

Frequency and severity of COVID-19 in multiple sclerosis: A short single-site report from northern Italy

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ABSTRACT

Neurologists are interested in understanding whether patients with multiple sclerosis (pwMS) undergoing immunomodulatory/immunosuppressive therapy are more susceptible to developing COVID-19 or have worse outcomes. Currently, there are no conclusive data in this regard. We report the prevalence and severity of COVID-19 (confirmed and possible) in pwMS followed at the Veneto Regional MS Center in Verona (Italy), an area most stricken by COVID-19. In our sample size, the prevalence of COVID-19 seems to be much higher than that officially reported at the regional level on the general population, but it also characterized by a favourable course.

Main text

From the first cases reported in China in December 2019, a form of severe acute respiratory distress syndrome due to SARS-CoV-2, a new human-infecting beta-coronavirus, became a global health threat.

Italy was the first western country affected by virus diffusion where the two first clusters of this new coronavirus disease (COVID-19) were identified in two neighbouring northern regions, Lombardy and Veneto. To date June 2nd, with the effect of a three-month-long lockdown, the number of new daily COVID-19 cases is no longer increasing, and its prevalence settles around 4 cases per 1000 inhabitants, mostly in northern Italy (Istituto superiore di sanità (ISS), 2020).

Notably, the clinical spectrum of COVID-19 is broad, and it appears to have a severe course mostly in people over 60 years of age and those with pre-existing risk conditions (Onder, 2020).

It is not yet fully established if pwMS are at increased risk of developing severe complications of COVID-19 even if positive initial data about it are coming (Sormani, 2020).

The present aims to report the frequency of COVID-19 in pwMS from the Veneto region, as well as report the level of immunosuppression determined by the ongoing treatment and informing about the outcome.

We have systematically collected data on the presence of symptoms compatible with COVID-19 in pwMS living in the Veneto region both by email-specific inhouse questionnaire sent to patients followed at Veneto MS regional centre of Verona and, partially, by self-reported new information. By implementing a daily phone-interview system, it was possible to monitor their clinical evolution.

COVID-19 was suspected in the presence of fever (temperature > 37.5 °C) plus at least one other compatible symptom. Confirmed COVID-19 was defined by a positive rt-PCR for SARS-CoV-2 on a nasopharyngeal swab. The temporary suspension of DMT was suggested in presence of COVID-19 symptoms (Giovannoni et al., 2020).

For each patient the latest blood chemistry findings (at most within six months) were retrieved from the medical records: the total number of lymphocytes, T- and B-cells were reported. A patient was considered immunosuppressed if the total number of lymphocytes was <1000/μL, or T-cells were <800/μL and/or B-cells <100/μL.

Among 1034 pwMS [765 females (F) and 269 males (M)], 29 (2.8%; 15F/14 M) have a confirmed- or possible COVID-19. None of these had demonstrated signs of MS activity within previous six months. Among these, 11 (1%; 4F/7 M) were confirmed COVID-19, while 18 (1.8%; 11F/7 M) showed symptoms highly suggestive of COVID-19 but were not established by rt-PCR (possible COVID-19). At the time of the current analysis, amongst the 5 million inhabitants of the Veneto region, 19.162 (0.4%) cases of COVID-19 were diagnosed (Portale Regione del Veneto Azienda Zero Emergenza Coronavirus SARS-CoV-2/COVID-19, 2020).

In the confirmed COVID-19 pwMS, the mean [SD] age was 49 (±4) years (range 43–55 years) with an apparent higher incidence in males.
Table 1
Demographic and clinical characteristics of pwMS with confirmed and possible COVID-19.

| pwMS Characteristics          | Confirmed COVID-19 | Possible COVID-19 | p-value | Total |
|-------------------------------|--------------------|-------------------|---------|-------|
| Age (years)                   | 49 ± 4             | 36 ± 10           | 0.001   | 39 ± 10 (23 - 58) |
| Gender F/M (tot)              | 4/7 (11)           | 11/7 (18)         | 0.067   | 15/14 (29)      |
| MS duration (years)           | 13.6 ± 6.6         | 7.9 ± 7.0         | 0.055   | 9.2 ± 6.7       |
| Relapsing MS (n/tot)          | 7/11               | 16/18             | 0.815   | 23/29           |
| Progressive MS (n/tot)        | 3/11               | 3/18              | 0.361   | 6/29            |
| EDSS (median, range)          | 4.0 (0–7.0)        | 2.0 (0–7.5)       | 0.112   | 2.5 (0–7.5)     |
| Comorbidities*                | 6/11               | 7/18              | 0.660   | 13/29           |

Data are reported as mean ± DS; EDSS reported as median (range min-max).
*Comorbidities include cardiovascular and lung disease, history of malignancy, smoking.

(7/269 M, 2.6%) than females (4/765F, 0.5%; p < 0.001).

These results were confirmed even if the possible COVID-19 cases were considered: 5.2% M (14/269) and 1.9% F (15/765; p < 0.001).

Immunosuppression was present in 11/29 (38%; 5 confirmed- and 6 possible) pwMS.

Hospitalization was required only in 2 male confirmed cases (18%; 2/11), because of high fever and dyspnea due to pneumonia (chest radiography of both patients showed typical ground-glass opacities; swab test was performed). These patients were on fingolimod and dimethyl fumarate (total lymphocytes at hospital admission, respectively, 610/μL and 1420/μL). They did not need intensive care given the stability of vital parameters during hospitalization and were discharged respectively 6- and 8-days later, after treatment with lopinavir/ritonavir or hydroxychloroquine. Their home-isolation continued without complication.

For all other 27 patients of which 10 were immunosuppressed (mean lymphocyte count of 815 ± 134 cell/μL), it was enough to take symptomatic drugs staying at home with an average duration of symptoms of 13 days (range 8–26 days).

Although no statistical analysis can be performed because of the small number of confirmed COVID-19 in our cohort to accurately compare our data with those of the general population of the Veneto region (based on confirmed cases), we observed a slightly lower, although not considerably different, prevalence of people who needed hospitalization or ICU admission: in the overall regional population, hospitalization has been requested in 30% (5545 people) of confirmed COVID-19 (vs 18% in our cohort, expected number of hospitalization 3) and ICU admission in 13% of them (vs 0% in our cohort, expected number of ICU admission 1) (Portale Regione del Veneto Azienda Zero Emergenza Coronavirus SARS-CoV-2/COVID-19, 2020). Overall no deaths were reported in our patients.

Despite derived from a small sample size, the frequency measure of COVID-19 in pwMS living in the Veneto region seems to be 2.5 times higher (1%; considering the confirmed cases of our cohort) than that reported in the inhabitants of the Veneto region (0.4%), leading to some interesting questions that need future investigations to be elucidated: are the pwMS more susceptible to SARS-CoV-2 infection or, simply, assuming that the individual risk of pwMS to develop COVID-19 who are not severely immunosuppressed (5/11 confirmed COVID-19 pwMS were moderately immunosuppressed with an average lymphocyte count of 640 ± 130 cell/μL) makes this similar to that of the general population? (Berger, 2020).

Therefore, considering this last point and the fact that everything we know on the state of infection comes only from laboratory-confirmed cases, further MS-population based studies, eventually using serological analysis, to be a potential good way to address the theory that currently we are underestimating the infection prevalence in the general population (Flaxman et al., 2020). In support of this, just consider that if we take into account 1% of confirmed + 1.8% of possible COVID-19, the prevalence of the infection is 2.8% in our cohort (7-times higher than that generally reported). As well as in the general population (range 45–64 years old) in our population we observed a prevalent involvement of the subjects over 45 years old, with more male than female cases requiring hospitalization (Portale Regione del Veneto Azienda Zero Emergenza Coronavirus SARS-CoV-2/COVID-19, 2020).

We not observed a specific DMT exposure which appears to be associated with a higher risk to experience COVID-19 or its complication even in presence in some cases of immunosuppression. However, we would also like to highlight the caution with which these finding must be read since the small sample size does not let an appropriate assessment of the DMT-related SARS-CoV-2 risk infection. Future studies on larger cohorts could identify DMTs at modify the risk of COVID-19 and perhaps associated with a favourable course even if in the presence of immunosuppression, thus emphasizing the hypothesis, also recently illustrated by Novi et al. (Novi et al., 2020), that immunosuppressant could be protective (certainly not in all clinical scenarios) against the acute respiratory distress syndrome (Chen et al., 2020). It is also possible that the younger age and the low disability physical status (median EDSS 2.5) might have contributed to mitigating the COVID-19 course in our cohort.

In addition to the availability of data only from a small pwMS group in the absence of a paired control group from which it is not possible to draw definite conclusions, the lack of swab confirmation in most cases (even if the probability of the infection remained very high in the presence of compatible clinical picture during the epidemic scenario) is the other main limitation of the present report, but which is worth noting is consistent with other previous observation (Monter-Escribano et al., 2020).

Declaration of Competing Interest

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Table 2
Disease-modifying treatment (DMT) and immune status at COVID-19 onset.

| DMT                                      | Confirmed COVID-19 | Possible COVID-19 | Total |
|------------------------------------------|--------------------|-------------------|-------|
| Dimethyl fumarate                        | 2/11               | 10/18             | 12/29 |
| Fingolimod                               | 3/11               | 1/18              | 4/29  |
| Natalizumab                              | 0/11               | 2/18              | 2/29  |
| Ocrelizumab                              | 3/11               | 4/18              | 7/29  |
| Teriflunomide                            | 1/11               | 1/18              | 2/29  |
| Azathioprine                             | 1/11               | 0/18              | 1/29  |
| No DMT                                   | 1/11               | 0/18              | 1/29  |
| Patients immunosuppressed*               | 5/11               | 6/18              | 11/29 (38%) |
| Total lymphocyte count (cell/μL) **      | 640 ± 130          | 590 ± 190         | 605 ± 222 |
| T-cells**                                | 555 ± 170          | 620 ± 274         | 580 ± 325 |
| B-cells**                                | 66 ± 24            | 48 ± 37           | 74 ± 58  |

Data are reported as mean ± DS.

One confirmed COVID-19 was not undergoing DMT; *A patient was considered immunosuppressed if the total number of lymphocytes was <1000/μL, or T-cells were <800/μL and/or B-cells <100/μL, irrespective of total lymphocytes count; **Lymphocytes count considering only immunosuppressed patients.
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