Real-time assessment of COVID-19 prevalence among multiple sclerosis patients: a multicenter European study

Gloria Dalla Costa 1,2 · Letizia Leocani 1,2 · Xavier Montalban 3 · Ana Isabel Guererro 3 · Per Soelberg Sørensen 4 · Melinda Magyar 4 · Richard J. B. Dobson 5,6 · Nicholas Cummins 7 · Vaibhav A. Narayan 8 · Matthew Hotopf 9 · Giancarlo Comi 1 · on behalf of the RADAR-CNS consortium

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Abstract
We assessed the prevalence and impact of COVID-19 among multiple sclerosis (MS) patients across Europe by leveraging participant data collected as part of the ongoing EU IMI2 RADAR-CNS major programme aimed at finding new ways of monitoring neurological disorders using wearable devices and smartphone technology. In the present study, 399 patients of RADAR-MS have been included (mean age 43.9 years, 60.7% females) with 87/399 patients (21.8%) reporting major symptoms suggestive of COVID-19. A trend for an increased risk of COVID-19 symptoms under alemtuzumab and cladribine treatments in comparison to injectables was observed. Remote monitoring technologies may support health authorities in monitoring and containing the ongoing pandemic.

Keywords Multiple Sclerosis · Remote monitoring technologies · COVID-19

Introduction
SARS-CoV-2 is a coronavirus first identified in December 2019 in China as the cause of a cluster of pneumonia cases (COVID-19 disease) of previously unknown etiology [1]. The virus has since spread globally, with the World Health Organization (WHO) declaring a pandemic state in March 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). However, the real prevalence and impact of the disease are unknown.

Remote Assessment of Disease and Relapse in Central Nervous System Disorders (RADAR-CNS) is an Innovative Medicine Initiative-funded project aimed at monitoring major depressive disorders, epilepsy, and multiple sclerosis (MS) using wearable devices and smartphone technology [2]. Through the ongoing remote monitoring of MS patients in...
Italy, Spain, and Denmark, we aimed to explore the prevalence and impact of the current pandemic among MS patients across Europe.

Methods

Study participants The MS work package of RADAR-CNS started recruiting in June 2018 with the aim to assess, through remote monitoring, the impact of MS on the emotional state of recently (< year) diagnosed patients and to monitoring disability and fatigue on relapsing-remitting (RRMS) and secondary progressive (SPMS) patients. Since then, passive (a smartwatch device and mobile sensors) and active monitoring strategies (questionnaires, cognitive, and physical tests) have been in place. Figure S1 shows the full inclusion criteria and assessment schemes. Approval of the protocol was obtained from hospitals’ ethical committees and informed consent obtained from all patients.

COVID-19 data A questionnaire to collect data systematically on COVID-19-related adverse events (Fig. S2) was sent to patients twice at a two-weekly interval (on March 25, 2020, and April 8, 2020, and data collected until April 15, 2020), through the RADAR-CNS active monitoring system. The results are based on the combination of the surveys. All data was managed by the open-source RADAR-based platform (www.radar-base.org) [2].

COVID-19 case definitions WHO guidelines define suspected cases as patients with fever, signs/symptoms of respiratory disease and travels/residence in a location reporting community transmission of COVID-19, or in contact with confirmed/probable COVID-19 cases in the 14 days prior to symptom onset, or people requiring hospitalization in the absence of alternative diagnosis [3]. As most of the confirmed COVID-19 cases do not fulfill these criteria [4] and considering the questionnaire was performed in areas with known community transmission of COVID-19, two alternative definitions were used: patients experiencing fever or anosmia/ageusia + any other COVID-19 symptoms, or respiratory symptoms + two other COVID-19 symptoms (case definition 1), and patients experiencing fever + any other COVID-19 symptoms, or respiratory symptoms + anosmia/ageusia (case definition 2). Laboratory-confirmed cases were included in both case definitions.

Statistical analysis Univariate and multivariate penalized likelihood logistic regression models (Firth method) have been used to assess predictors of COVID-19 occurrence [5]. The impact of MS treatments on COVID-19 risk was first evaluated separately for each drug (Fig. S3) and then analyzed according to the following treatment groups: injectables (interferons and glatiramer acetate), oral treatments (dimethyl fumarate, teriflunomide), fingolimod, natalizumab, anti-CD20 (ocrelizumab), immune system resetting drugs (alemtuzumab, cladribine). p values < 0.05 were deemed statistically significant. Computing environment R was used for all statistical analyses (R Development Core Team, 2005).

Results

Cohort baseline characteristics (Table 1)

As of March 1, 2020, 499 patients have been enrolled in the RADAR-MS studies and 403 (81%) remained under active and passive remote monitoring. The COVID-19 questionnaire was completed at least once by 399 patients (99%).

| Characteristic                        | n = 399 |
|--------------------------------------|---------|
| Age, years                           | 43.9 ± 10.7 |
| Sex, n (%)                           |         |
| Females                              | 242 (60.7) |
| Males                                | 157 (39.3) |
| Smokers                              | 84 (21.1) |
| BMI                                  | 24.47 ± 5.7 |
| Healthcare workers                   | 19 (4.7) |
| Course of disease, n (%)             |         |
| Clinically isolated syndromes        | 5 (1.3)  |
| Relapsing-remitting                  | 305 (76.4) |
| Secondary progressive                | 89 (22.3) |
| Disease duration, years              | 13.1 ± 10.3 |
| Expanded Disability Status Scale     | 3.5 (2.0–4.0) |
| Presence of comorbidities, n (%)     | 144 (36.1) |
| Cardiovascular/hypertension          | 51 (12.8) |
| Diabetes                             | 5 (1.3)  |
| COPD                                 | 1 (0.3)  |
| Malignancies                         | 2 (0.5)  |
| Ongoing MS treatments, n (%)         | 359 (90) |
| Interferons/glatiramer acetate       | 81 (20.3) |
| Dim. fumarate/teriflunomide          | 108 (27.1) |
| Natalizumab                          | 44 (11.0) |
| Fingolimod                           | 67 (16.8) |
| Anti-CD20                            | 44 (11.0) |
| Alemtuzumab/cladribine               | 15 (3.8)  |
| Other ongoing treatments, n (%)      | 237 (59.4) |
| Vitamin D supplements                | 40 (10.0) |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; MS, multiple sclerosis; DMD, disease-modifying drugs; mean ± standard deviation; number (percentage)
Prevalence and predictors of COVID-19 by case definition

Major symptoms suggestive of COVID-19 infection have been reported by 87 patients (21.8%, 95% CI 17.8–25.9). Among these, 31 (7.8%) had a fever, 73 (18.3%) had respiratory symptoms, 38 (9.5%) had gastrointestinal disturbances, 17 (4.3%) had conjunctivitis, and 17 (4.3%) experienced ageusia and anosmia. Two patients had COVID-19 pneumonia, and one patient was hospitalized. No one died of COVID-19.

In the cohort, 52 patients (13.0%, 95% CI 9.7–16.3) met the case definition 1, and 37 (9.3%, 95% CI 6.4–12.1) met the case definition 2 criteria.

Ten patients were tested for SARS-CoV-2 through nasopharyngeal swab: four of them were positive, and one tested negative but had COVID-19 pneumonia upon X-ray examination and swab test which was performed 26 days after symptom onset. Figure S4 shows the occurrence of suspected COVID-19 cases.

Patients with SPMS were at lower risk than relapsing-remitting MS of fulfilling either definitions (case definition 1: OR 0.36 (0.13–0.84); case definition 2: OR 0.23 (0.05–0.71), p < 0.01 for all cases, Table 1). A trend for patients on cladribine/alemtuzumab to be more likely classified as COVID-19 cases than patients with injectables was observed, independently of age, sex, and disease course (case definition 1: OR 3.78 (1.00–15.93), p 0.05; case definition 2: OR 4.87 (1.10–21.04), p 0.04, Fig. 1, Table S2).

Impact of COVID on MS patients

Changes in daily activities because of COVID-19 were reported by 344 patients (86%): 148 (37%) started working from home, 66 (17%) took care of children, and four (1%) cared for a sick relative. No outdoor hobbies or social activities were reported by 228 patients (57%), and the daily average time spent outside was 1.8 h. On the emotional level, 132 patients (33%) were deeply worried by the pandemic, 233 (58%) moderately worried, and 32 (8%) were unaffected.

Discussion

A number of newly diagnosed COVID-19 cases are updated daily (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports), but these are clearly
underestimated [6] as diagnosis depends on local availability of the test. In our study, five confirmed COVID-19 cases (four with positive swab tests and one patient with COVID-19 pneumonia) were reported (1.3%); a low prevalence as just ten patients (2.5%) of the cohort were tested for the virus. Using different case definitions, the percentage of MS patients with symptoms suggestive of infection varied between 9 and 13%. These figures align with a recent study suggesting that the prevalence of the disease in Europe, in particular Italy, maybe nine times higher than officially reported [6]. According to our results, there is no evidence of a worse COVID-19 evolution in patients affected by MS: two patients only developed pneumonia and one was hospitalized. Global data indicates that morbidity is lower in younger COVID-19 patients [7], as our data also suggests. Patients with SPMS had a lower risk of infection compared with RRMS, maybe because they are less treated and with less-frequent social contacts. Disease-modifying treatments did not significantly change the risk and severity of COVID-19; however, a trend for an increased risk of infection with immune-resetting drugs (alemtuzumab and cladribine) was observed compared with injectables, despite low numbers prevent any definite conclusion. This aligns with previous studies showing a generally increased risk of infections with cladribine and alemtuzumab [8, 9]. The COVID-19 pandemic has had a heterogeneous impact in different countries. Our patients come from highly affected areas in Europe; therefore, our results may be partially representative of the general MS population. However, the study highlights the importance of remote monitoring technologies that have shed some light on the impact of COVID-19 in our MS patients in real time and may provide support to health authorities in monitoring and containing the pandemic.

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Compliance with ethical standards Approval of the protocol was obtained from hospitals’ ethical committees and informed consent obtained from all patients.

Conflict of interest V.A.N. is an employee of Janssen Research & Development LLC and may own equity in the company.

Disclaimer This communication reflects the views of the RADAR-CNS consortium, and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein.

Data sharing The scientific data used in this paper is collected under the project: EU/EFPIA IMI RADAR-CNS (grant agreement no. 115902). The data usability and sharing are performed under the agreed guidelines of the RADAR-CNS consortium. The anonymized data will be shared upon request subject to RADAR-CNS consortium approval. Pending the aforementioned approval, data sharing will be made in a secure setting, on a per-case-specific manner. Please submit such requests to the corresponding author of the paper. The shared data cannot be used for publication purposes without the explicit consent of the RADAR-CNS consortium. The additional related documents are available (e.g., study protocol, statistical analysis plan, informed consent form) upon request.

References
1. Zhou P, Yang XL, Wang XG et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579(7798):270–273
2. Ranjan Y, Rashid Z, Stewart C et al (2019) RADAR-base: open source mobile health platform for collecting, monitoring, and analyzing data using sensors, wearables, and mobile devices. JMIR Mhealth Uhealth 7(8):e11734
3. World Health Organization (2020) Surveillance case definitions for human infection with novel coronavirus (nCoV): interim guidance v1, January 2020. World Health Organization. https://apps.who.int/iris/handle/10665/330376, License: CC BY-NC-SA 3.0 IGO. Accessed 1 Jul 2020
4. Huang C, Wang Y, Li X et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497–506
5. Firth D (1993) Bias reduction of maximum likelihood estimates. Biometrika [Internet]. 80(1):27–38
6. Lachmann A, Jagodnik KM, Giorgi FM, Ray F Correcting under-reported COVID-19 case numbers: estimating the true scale of the pandemic. medRxiv 2020.03.14.20036178. https://doi.org/10.1101/2020.03.14.20036178
7. Republic of Korea Center of Disease Control. Updates on COVID-19 in Republic of Korea, 3/13/2020.
8. Giovannoni G, Comi G, Cook S et al (2010) A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 362:416–426
9. Cohen JA, Coles AJ, Arnold DL et al (2012) Alemtuzumab versus interferon beta-1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380:1819–1828

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