Incidence, clinical characteristics, risk factors and outcomes of meningoencephalitis in patients with COVID-19

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Abstract
We investigated the incidence, clinical characteristics, risk factors, and outcome of meningoencephalitis (ME) in patients with COVID-19 attending emergency departments (ED), before hospitalization. We retrospectively reviewed all COVID patients diagnosed with ME in 61 Spanish EDs (20% of Spanish EDs, COVID-ME) during the COVID pandemic. We formed two control groups: non-COVID patients with ME (non-COVID-ME) and COVID patients without ME (COVID-non-ME). Unadjusted comparisons between cases and controls were performed regarding 57 baseline and clinical characteristics and 4 outcomes. Cerebrospinal fluid (CSF) biochemical and serologic findings of COVID-ME and non-COVID-ME were also investigated. We identified 29 ME in 71,904 patients with COVID-19 attending EDs (0.40‰, 95% CI = 0.27–0.58). This incidence was higher than that observed in non-COVID patients (150/1,358,134, 0.11‰, 95% CI = 0.09–0.13; OR=3.65, 95%CI=2.45–5.44). With respect to non-COVID-ME, COVID-ME more frequently had dyspnea and chest X-ray abnormalities, and neck stiffness was less frequent (OR=0.3, 95%CI=0.1–0.9). In 69.0% of COVID-ME, CSF cells were predominantly lymphocytes, and SARS-CoV-2 antigen was detected by RT-PCR in 1 patient. The clinical characteristics associated with a higher risk of presenting ME in COVID patients were vomiting (OR=3.7, 95%CI=1.4–10.2), headache (OR=24.7, 95%CI=10.2–60.1), and altered mental status.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is predominantly characterized by lower respiratory tract and cardiovascular system involvement. However, possible neurological symptoms have been described, such as headache, dizziness, hypogeusia, or neuralgia, even in up to 36.4% of the patients [1]. Nevertheless, the symptoms described are common in many infections and could represent disturbances in neurological function rather than neurological disease. Anosmia and ageusia have received much attention, but are ubiquitous in other common upper respiratory tract infections [2]. Some neurological complications of COVID-19, including meningoencephalitis (ME), have been previously described as case reports [3–5].

Connections between viral infections and central nervous system (CNS) pathologies are not new. Coronaviruses are not a common cause of neurological disease, but members of coronaviridae have already demonstrated the ability to produce neurological symptoms, including brain inflammation and encephalomyelitis, as well as presumed parainfectious disorders [2, 6–9]. Detection of SARS-CoV RNA in the CSF of a patient with SARS has been reported [10]. However, the pathophysiological mechanism of illness and the relationship between COVID-19 and CNS involvement remain unclear. The relative expression of the two key co-receptors for SARS-CoV-2 entry, ACE2, and TMPRSS2 has been described across multiple tissues and highlights that there is minimal expression in brain tissue, suggesting that direct brain infection would not be a common phenomenon. The one brain cell type, which does express both genes, is the oligodendrocyte, and therefore, SARS-CoV-2 encephalitis, when present, might be expected to be a predominantly white matter disease [2]. Experimental and clinical studies suggest brainstem involvement and the potential for transneuronal virus transmission in addition to misdirected host immune responses [11].

The real incidence of ME in patients with COVID-19 is currently unknown. There are some sporadically reported cases in patients with COVID-19 [3–5]. In order to further investigate these aspects, we designed the present study with the following specific objectives: (1) to determine the frequency of ME patients with COVID-19; (2) to describe whether there is any distinctive clinical characteristic in these patients in comparison with ME observed in non-COVID patients; (3) to uncover risk factors associated with the development of ME in patients with COVID-19; and (4) to investigate the outcomes of COVID patients presenting ME.

Methods

Study design and setting

The present study forms part of the Unusual Manifestations of Covid-19 (UMC-19) project, which was designed to investigate the potential relationship between COVID-19 and 10 different entities that could be influenced by SARS-CoV-2 infection itself: Guillain-Barre syndrome, spontaneous pneumothorax, acute pancreatitis, meningoencephalitis, (myo)pericarditis, acute coronary syndrome, deep venous thrombosis, pulmonary embolism, ictus, and gastrointestinal bleeding. The main objectives of the UMC-19 project were common for all entities, and consisted in the description of incidence, risk factors, clinical characteristics, and outcomes for each particular entity, using as comparators COVID patients that did not develop this entity as well as non-COVID patients that did present the entity. Details of the project have been extensively presented elsewhere [12].

In Spain, the first case of SARS-CoV-2 infection was detected on January 31st, 2020, and, accordingly, the definition of the COVID period for patient inclusion in the present study was set from March 1st to April 30th, 2020 [13]. During this 61-day period, 213,435 cases of COVID-19 were confirmed in Spain by the Ministry of Health [14]. For the recruitment of controls, the UMC-19 project selected patients from two different periods: one corresponding to the same dates as the cases (from March 1st to April 30th, 2020) and one corresponding to same period of the previous year (from March 1st to April 30th, 2019).

The investigators of the UMC-19 project initially contacted 152 Spanish EDs, which roughly constitute half of the 312 hospital EDs of the Spanish public health network. Of these, 81 were interested in participating and analyzed the protocol, and finally 61 (20% of Spanish EDs) consented to participate.

Keywords Meningoencephalitis · COVID-19 · SARS-Cov-2 · Incidence · Clinical characteristics · Risk factors · Outcome
and sent all the required data in due time (Fig. 1). Altogether these 61 hospitals provide health coverage to 15.2 million citizens (32% of the population of 46.9 million of Spain) and make up a balanced representation of the Spanish territory (representing 12 of the 17 Spanish autonomous communities), type of hospital (community, reference, and high-technology university hospitals were included), and involvement in pandemic (with EDs attending from 1 to 47% of the ED census during the COVID outbreak period corresponding to COVID patients) [12].

The investigation of ME in COVID patients, one of the entities included in the UMC-19 project, was labeled as UMC-19 Study 3 (UMC-19-S3) and consisted in a retrospective, multicenter, case-control study that reviewed the medical reports of COVID patients who attended at Spanish EDs and who were diagnosed as having ME during ED assessment and management, before hospitalization.

**Cases of the UMC-19-S3**

The case group was formed by COVID patients diagnosed with ME made on the basis of clinical presentation, lumbar puncture, abnormality on electroencephalography, and CT scan. All meningoencephalitis cases fulfill the consensus definition of encephalitis by the International Encephalitis Consortium [15], and other etiologies were rule out. As we wanted to investigate the role of SARS-CoV-19 in such unusual manifestations, before the patient was hospitalized and treatment with specific drugs had been initiated, the possible meningoencephalitis cases diagnosed during hospitalization were excluded. On the other hand, due to the shortage in all kind of diagnostic tests during the pandemic outbreak, diagnosis of COVID was accepted based on SARS-Cov-2 RNA detection in a nasopharyngeal swab by reverse transcriptase polymerase chain reaction (RT-PCR), a clinically compatible clinical picture, or the presence of the typical lung parenchymal infiltrates in chest X-ray or pulmonary CT in patients with some clinical symptoms attributable to COVID. Diagnostic adjudication was made by the principal investigator of each center, without external review.

**Controls of the UMC-19-S3**

We defined two different control groups. One group was formed by all non-COVID patients with a diagnosis of ME attending the ED during the same period as the cases (March 1st to April 30th, 2020), which was defined in the same terms as cases. In order to avoid that some of these control cases could eventually have inadvertent infection by SARS-Cov-2, in this group, we also included all patients with ME diagnosed in the ED from March 1st to April 30th, 2019, just 1 year before the COVID pandemic. This group, named non-
COVID-ME (control group A), was specifically designed to uncover the particular distinctive clinical characteristics of ME developed in COVID patients with respect to ME developed in the general population.

The second control group was formed by COVID patients (without ME) attending the ED during the same period of the COVID outbreak used for case inclusion (March 1st to April 30th, 2020). This group was formed by selecting 10 COVID patients for every case detected by each center. Selection was randomly performed by the inclusion of the 5+5 COVID patients seen immediately before and after each case included by the center. This group, named COVID-non-ME (control group B), was specifically designed to determine the risk factors for ME development in COVID patients.

Independent variables

We collected 57 independent variables, which included 2 demographic data (age, sex), 12 comorbidities (chronic obstructive pulmonary disease, asthma, active smoker, hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, obesity—clinically estimated, cerebrovascular disease, chronic kidney disease—creatinine >2 mg/dL, dementia, active cancer), 26 signs and symptoms recorded at ED arrival (time elapsed since symptoms started to ED attendance, fever, rhinorrhea, cough, expectoration, dyspnea, chest pain, abdominal pain, vomiting, diarrhea, altered mental status, headache, anosmia, dysgeusia, meningeal signs (neck stiffness, Kernig’s sign, and Brudzinski’s sign), Glasgow coma scale, temperature, systolic blood pressure, heart rate, respiratory rate, room air pulsioxymetry, rhonchus, whistles, rales), 13 laboratory parameters (C-reactive protein (CRP), creatinine, sodium, potassium, aspartate amino transferase (AST), bilirubin, lactate dehydrogenase (LDH), procalcitonin, hemoglobin, leucocytes, lymphocytes, platelets, D-dimer), and 4 radiological findings in chest X-ray (cardiomegaly, lung interstitial infiltrates, ground-glass opacities, and pleural effusion). For the cases and control group A patients, we also reviewed data from cerebrospinal fluid (CSF) analysis, including glucose, proteins, cells, and microbiological results.

Outcomes

We defined 4 different outcomes for cases and controls consisting in (1) the need for hospitalization; (2) the need to be admitted to an intensive care unit (ICU); (3) prolonged hospitalization (defined as a length of stay >7 days, which is the median length of stay of hospitalized patients in Spain); and (4) in-hospital all-cause mortality.

Statistical analysis

Discrete variables were expressed as absolute values and percentages, and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR) if not normally distributed. Incidences were expressed as cases per thousand patients (‰) with 95% confidence interval (CI). Differences between case group and controls groups were assessed by the chi-square test (or Fisher exact test if needed) for qualitative variables, and Student’s t test (or the Mann-Whitney non-parametric test if non-normally distributed) for quantitative variables. The magnitude of associations was expressed as unadjusted odds ratio (OR) with 95% CI (for continuous variables, associations were dichotomized using clinically meaningful cutoffs). As the number of cases expected to be identified was not large, we did not plan to go further in the investigation of the significant relationships identified in the unadjusted analysis by using adjusted models.

In all comparisons, statistical significance was accepted if the p value was < 0.05 or if 95% CI of the risk estimations excluded the value 1. The analyses were performed with the SPSS (v.24) statistical software package (IBM, Armonk, NY, USA).

Ethics

The UMC-19 project was approved by the Ethics Committee of the Hospital Clinic of Barcelona (Spain), with the reference number HCB/2020/0534, that acted as the central ethical committee. Under the exceptional circumstances generated by the COVID-19, the urgent need to obtain feasible data related to this new disease, and the non-interventional and retrospective nature of the project, obtaining of written permission from patients to be included in the study was waived. All the patients were codified by investigators of the participating centers before their data were entered into the general database, as patient identity remained anonymous for investigators who analyzed the database. The UMC-19-S3 was carried out in strict compliance with the Declaration of Helsinki principles. The authors designed the study, gathered and analyzed the data, vouched for the data and analysis, wrote the paper, and decided to publish.

Results

EDs attended 486,833 patients (average of 131 patients/day/ED), and 71,904 (14.8%) were diagnosed with COVID-19. On the other hand, during the pre-COVID phase of the study, 943,205 patients were seen in the ED (average of 253 patients/day/ED). Patient inclusion in each group is presented in Fig. 1. We identified 29 ME in COVID patients (frequency=0.40‰, 95%CI=0.27–0.58), and these individuals constituted the case
Among the remaining 1,358,134 non-COVID patients attended in EDs, 150 were diagnosed as having ME (frequency = 0.11‰, 95% CI = 0.09–0.13). These patients constituted control group A (non-COVID-ME). In comparison to non-COVID patients coming to the ED, COVID patients exhibited a significantly higher frequency of ME (OR = 3.65, 95% CI = 2.45–5.44). On the other hand, control group B was made up of 290 randomly selected COVID patients without ME (COVID-non-ME) during the same period. Infection by SARS-CoV-2 was confirmed by RT-PCR in 48.3% and 74.8% of patients in the case group and control group B, respectively (p = 0.002). Regarding the diagnosis of COVID patients in the COVID-ME patients with a negative RT-PCR result, this was based on the presence of respiratory symptoms with interstitial lung infiltrates or ground-glass lung opacities in the X-ray or pulmonary CT.

The mean age of the case group was 57.0 (SD 23.1) years and 17 (58.6) were female. The remaining baseline characteristics of these patients are shown in Table 1. Compared to non-COVID-ME, case group patients more frequently had dyspnea and chest X-ray abnormalities (Tables 1, 2, 3, and 4). Neck stiffness was less frequent in COVID-ME patients that in non-COVID-ME. From the analytical point of view, COVID-ME patients more frequently had increased in CRP, LDH, and D-dimer levels, and decreased leucocyte and lymphocyte counts. The biochemistry and cell pattern of CFS are described in Table 3, being similar in both groups. Regarding microbiological findings in the CFS, it should be highlighted that after cultures, antigen testing, and multiplex PCR, no microbiological diagnosis was achieved in patients with COVID infection, except one patient who was RT-PCR positive for SARS-CoV-2 in CSF (Table 3).

When we compared cases with control group B patients, we observed that headache (OR 24.7, 95% CI 10.165–60.149), altered mental status (OR 12.864, 95% CI 6.615–25.016), neck stiffness (OR 12.154, 95% CI 8.410–17.564), and vomiting (OR 3.7, 95% CI 1.353–10.234) were associated with a higher risk of ME in COVID patients. Respiratory symptoms were more frequent in COVID-non-ME patients than in COVID-ME patients (Tables 1, 2, 3, and 4).

Comparing the case group with control group A, the need for hospitalization was present in 28 (96.6%) COVID-ME patients and in 148 (98.7%) non-COVID-ME patients (p = 0.417), while admission to the ICU occurred in 12 (42.9%) COVID-ME patients and in 39 (26.4%) non-COVID-ME patients (p = 0.077). In addition, hospitalization longer than 7 days was observed in 13 (44.8%) COVID-ME patients and in 53 (35.3%) non-COVID-ME patients.

Table 1 Baseline characteristics of patients with COVID-19 with meningoencephalitis and comparison with patients without COVID-19 with meningoencephalitis (control group A) and with patients with COVID-19 without meningoencephalitis (control group B).

|                          | Cases (COVID-ME) N=29 | Control group A (non-COVID-ME) N=150 | Control group B (COVID-non-ME) N=290 | p value1 | p value2 |
|--------------------------|------------------------|--------------------------------------|--------------------------------------|----------|----------|
| Demographics             |                        |                                      |                                      |          |          |
| Age (years) [median (IQR)] | 63 (39–75)           | 54 (32–73)                           | 64 (51–77)                           | 0.235    | 0.329    |
| Sex (female)             | 17 (58.6)              | 66 (44.0)                            | 136 (46.9)                           | 0.214    | 0.248    |
| Comorbidities            |                        |                                      |                                      |          |          |
| Hypertension             | 13 (44.8)              | 58 (38.7)                            | 135 (46.6)                           | 0.535    | 0.859    |
| Dyslipidemia             | 11 (37.9)              | 42 (28.0)                            | 97 (33.4)                            | 0.284    | 0.627    |
| Diabetes mellitus        | 6 (20.7)               | 37 (24.7)                            | 52 (17.9)                            | 0.646    | 0.713    |
| Active smoker            | 4 (13.8)               | 29 (19.3)                            | 20 (6.9)                             | 0.460    | 0.355    |
| Asthma                   | 3 (10.3)               | 7 (4.7)                              | 20 (6.9)                             | 0.233    | 0.494    |
| Coronary artery disease  | 2 (6.9)                | 7 (4.7)                              | 22 (7.6)                             | 0.615    | 0.893    |
| Obesity (clinically estimated) | 2 (6.9)         | 21 (14.0)                            | 45 (15.5)                            | 0.295    | 0.212    |
| Chronic kidney disease   | 2 (6.9)                | 5 (3.3)                              | 19 (6.6)                             | 0.365    | 0.943    |
| Immunosuppression        | 2 (6.9)                | 7 (4.7)                              | 14 (4.8)                             | 0.615    | 0.626    |
| Cerebrovascular disease  | 1 (3.4)                | 12 (8.0)                             | 20 (6.9)                             | 0.387    | 0.475    |
| Dementia                 | 1 (3.4)                | 7 (4.7)                              | 25 (8.6)                             | 0.771    | 0.332    |
| Active cancer            | 1 (3.4)                | 16 (10.7)                            | 27 (9.3)                             | 0.225    | 0.287    |
| Chronic obstructive pulmonary disease | 0 (0)                  | 8 (5.3)                              | 26 (9.0)                             | 0.203    | 0.092    |

1 p values refer to comparison between cases and control group A
2 p values refer to comparison between cases and control group B
ME, meningoencephalitis; IQR, interquartile range
Table 2  Clinical and analytical characteristics of the acute episode of patients with COVID-19 with meningoencephalitis and comparison with patients without COVID-19 with meningoencephalitis (control group A) and with patients with COVID-19 without meningoencephalitis (control group B)

| Symptoms at ED arrival | Cases (COVID-ME) N=29 | Control group A (non-COVID-ME) N=150 | Control group B (COVID-non-ME) N=290 | p value1 | p value2 |
|------------------------|------------------------|--------------------------------------|--------------------------------------|----------|----------|
| Lasting symptoms (days) [median (IQR)] | 3 (17) | 2 (1–6) | 7 (4–10) | 0.183 | 0.003 |
| Fever | 18 (62.1) | 80 (53.3) | 163 (56.2) | 0.387 | 0.544 |
| Rhinorrhea | 1 (3.4) | 9 (6.0) | 20 (6.6) | 0.584 | 0.475 |
| Cough | 3 (10.3) | 5 (3.3) | 171 (59.0) | 0.094 | <0.0001 |
| Expectoration | 1 (3.4) | 12 (8.0) | 42 (14.5) | 0.387 | 0.097 |
| Dyspnea | 7 (24.1) | 5 (3.3) | 166 (57.2) | <0.0001 | 0.001 |
| Chest pain | 3 (10.3) | 5 (3.3) | 38 (13.1) | 0.094 | 0.672 |
| Abdominal pain | 3 (10.3) | 5 (3.3) | 16 (5.5) | 0.094 | 0.295 |
| Vomiting | 6 (20.7) | 40 (26.7) | 19 (6.6) | 0.500 | 0.007 |
| Diarrhea | 3 (10.3) | 12 (8.0) | 50 (17.2) | 0.677 | 0.341 |
| Altered mental status | 18 (62.1) | 85 (56.7) | 18 (6.2) | 0.590 | <0.0001 |
| Headache | 12 (41.4) | 86 (57.3) | 35 (12.1) | 0.114 | <0.0001 |
| Anosmia | 1 (3.4) | 0 (0) | 21 (7.2) | 0.023 | 0.442 |
| Dysgeusia | 0 (0) | 1 (0.7) | 22 (7.6) | 0.659 | 0.124 |
| Seizure | 4 (13.8) | 17 (11.3) | 0 (0) | 0.706 | <0.0001 |
| Neck stiffness | 3 (10.3) | 49 (32.7) | 0 (0) | 0.015 | <0.0001 |
| Kernig’s sign | 1 (3.4) | 23 (15.3) | 0 (0) | 0.086 | 0.002 |
| Brudzinski’s sign | 1 (3.4) | 24 (16.0) | 0 (0) | 0.074 | 0.002 |
| Signs at ED arrival [median (IQR)] | 37.3 (36.4–37.7) | 37.2 (36.2–38.0) | 36.6 (36.0–37.3) | 0.822 | 0.010 |
| Temperature (°C) | 125 (102–143) | 131 (114–151) | 126 (113–140) | 0.142 | 0.551 |
| SBP (mmHg) | 100 (80–109) | 90 (78–108) | 88 (78–100) | 0.387 | 0.043 |
| Heart rate (bpm) | 18 (16–21) | 16 (14–20) | 18 (16–23) | 0.017 | 0.955 |
| Respiratory rate (bpm) | 96 (91–98) | 98 (95–99) | 96 (93–98) | 0.032 | 0.724 |
| Room air pulsoxymetry (%) | 96 (91–98) | 98 (95–99) | 96 (93–98) | 0.032 | 0.724 |
| Laboratory findings [median (IQR)] | 4.0 (1.6–10.9) | 1.6 (0.4–6.5) | 5.9 (1.9–12.0) | 0.045 | 0.468 |
| C-reactive protein (mg/dL) | 0.8 (0.7–1.0) | 0.8 (0.6–1.0) | 0.9 (0.7–1.1) | 0.414 | 0.260 |
| Creatinine (mg/dL) | 138 (134–140) | 138 (135–140) | 138 (136–140) | 0.784 | 0.422 |
| Sodium (mmol/L) | 3.8 (3.6–4.2) | 4.0 (3.7–4.4) | 4.0 (3.7–4.4) | 0.118 | 0.044 |
| Potassium (mmol/L) | 26 (17–44) | 24 (17–36) | 30 (22–45) | 0.425 | 0.203 |
| Aspartate amino transferase (IU/L) | 0.7 (0.4–1.0) | 0.5 (0.4–0.9) | 0.5 (0.4–0.7) | 0.903 | 0.218 |
| Bilirubin (mg/dL) | 275 (198–483) | 207 (158–263) | 270 (205–346) | 0.020 | 0.574 |
| Lactate dehydrogenase (IU/L) | 0.16 (0.11–1.06) | 0.12 (0.06–1.3) | 0.10 (0.05–0.18) | 0.457 | 0.028 |
| Procalcitonin (ng/mL) | 13 (12–15) | 13 (12–15) | 13.8 (12.6–14.8) | 0.968 | 0.921 |
| Hemoglobin (g/L) | 8.7 (5.0–11.8) | 10.6 (7.8–14.6) | 6.6 (4.9–9.1) | 0.008 | 0.191 |
| Leucocytes count (cells/μL) | 1.05 (0.70–1.67) | 1.4 (1.0–2.3) | 1.1 (0.8–1.6) | 0.018 | 0.550 |
| Lymphocytes | 203 (144–310) | 235 (182–296) | 212 (164–263) | 0.274 | 0.932 |
| Platelets (cells/μL) | 898 (570–2770) | 622 (366–1596) | 620 (360–1272) | 0.138 | 0.036 |
| D-dimer (mg/mL) | 25 (86.2) | 118 (78.7) | 280 (96.6) | 0.354 | 0.010 |
| Chest X-ray | 1 (4.0) | 16 (14.8) | 28 (10.4) | 0.114 | 0.304 |
| Cardiomegaly | 11 (44.0) | 7 (6.0) | 113 (40.4) | <0.001 | 0.772 |
| Interstitial lung infiltrates | 10 (40.0) | 5 (4.3) | 160 (57.1) | <0.001 | 0.098 |
| Pleural effusion | 2 (8.0) | 3 (2.7) | 12 (4.4) | 0.208 | 0.415 |

1 p values refer to comparison between cases and control group A
2 p values refer to comparison between cases and control group B
ME, meningoencephalitis; IQR, interquartile range; SBP, systolic blood pressure; ED, emergency department
p values in bold denote statistically significant differences (p<0.05)

(p=0.332). There were 7 (24.1%) deaths in the COVID-ME patients while there were 16 (10.7%) in non-COVID-ME patients (p=0.047). Regarding comparison of the case group with control group B, the need for hospitalization was present in 28 (96.6%) COVID-ME patients and in 220 (75.9%) COVID-non-ME patients (p=0.011), while admission to an ICU was observed in 12 (42.9%) COVID-ME patients and in 16 (7.3%) COVID-non-ME patients (p<0.001). Hospitalization longer than 7 days was shown in 13 (44.8%) COVID-ME patients and in 80 (27.6%) COVID-non-ME patients.
patients \((p=0.051)\), and there were 7 (24.1%) deaths among COVID-ME patients compared to 48 (16.6%) in COVID-non-ME patients \((p=0.302)\). Nonetheless, we only detected statistically significant differences in case outcomes with respect to in-hospital mortality, which was higher than in non-COVID-ME patients \((\text{OR}=2.158; 95\%\text{CI}=1.041–4.475)\). There were also statistically significant differences in the need for hospitalization \((\text{OR}=8.016; 95\%\text{CI}=1.190–\)

| Lumbar puncture                                    | Cases (COVID-ME) | Control group A (non-COVID-ME) | \(p\) value |
|----------------------------------------------------|------------------|--------------------------------|-------------|
| Decreased CSF pressure \((<10\;\text{H}_2\text{O}\;\text{cm})\) | 1 (3.4)          | 12 (8.0)                       | 0.711       |
| Increased CSF pressure \((>20\;\text{H}_2\text{O}\;\text{cm})\) | 1 (3.4)          | 4 (2.7)                        | 0.508       |
| Glucorachia [median (IQR)]                        | 67 (52–84)       | 63 (48–83)                     | 0.306       |
| Proteinorachia [median (IQR)]                     | 76 (44–106)      | 70 (40–132)                    | 0.786       |
| Nucleated cells [median (IQR)]                    | 51 (25–119)      | 86 (20–346)                    | 0.135       |
| Polymorphonuclears [median (IQR)]                 | 10 (4–32)        | 14 (2–85)                      | 0.684       |
| Lymphocytes [median (IQR)]                        | 25 (3–68)        | 20 (6–88)                      | 0.821       |
| Lymphocyte predominance                           | 20 (69.0)        | 81 (54.0)                      | 0.136       |

| Microbiological findings in CSF [\(n\;\%\)]      | Cases (COVID-ME) | Control group A (non-COVID-ME) | \(p\) value |
|----------------------------------------------------|------------------|--------------------------------|-------------|
| Streptococcus pneumonia                            | 0 (0)            | 21 (14.0)                      | 0.032       |
| Herpes simplex virus                               | 0 (0)            | 9 (6.0)                        | 0.175       |
| Enteroviruses                                      | 0 (0)            | 5 (3.3)                        | 0.318       |
| Mycobacterium tuberculosis                        | 0 (0)            | 4 (2.6)                        | 0.373       |
| Varicella-zoster virus                             | 0 (0)            | 4 (2.6)                        | 0.373       |
| Neisseria meningitidis                             | 0 (0)            | 3 (2.0)                        | 0.442       |
| Haemophilus influenza                              | 0 (0)            | 3 (2.0)                        | 0.442       |
| Listeria monocytogenes                             | 0 (0)            | 3 (2.0)                        | 0.442       |
| Staphylococcus aureus                              | 0 (0)            | 1 (0.7)                        | 0.659       |
| Propionibacterium acnes                            | 0 (0)            | 1 (0.7)                        | 0.659       |
| Epstein bann                                       | 0 (0)            | 1 (0.7)                        | 0.659       |
| Streptococcus agalactiae                           | 0 (0)            | 1 (0.7)                        | 0.659       |
| Influenza virus                                    | 0 (0)            | 1 (0.7)                        | 0.659       |
| Cryptococcus neoformans                            | 0 (0)            | 1 (0.7)                        | 0.659       |
| Escherichia coli                                   | 0 (0)            | 1 (0.7)                        | 0.659       |
| All microbiological tests negative                  | 29 (100)         | 91 (60.6)                      | <0.001      |

| SARS-CoV-2 RT-PCR result in CSF                    | Cases (COVID-ME) | Control group A (non-COVID-ME) | \(p\) value |
|----------------------------------------------------|------------------|--------------------------------|-------------|
| Positive                                           | 1 (3.5)          | 0 (0)                           | 0.022       |
| Negative                                           | 9 (31.0)         | 15 (10)                         | 0.002       |
| Not done                                           | 19 (65.5)        | 135 (90)                        | <0.001      |

| Final etiological diagnosis of the ME              | Cases (COVID-ME) | Control group A (non-COVID-ME) | \(p\) value |
|----------------------------------------------------|------------------|--------------------------------|-------------|
| Bacterial                                           | 0                | 34                              | 0.004       |
| Tuberculous                                        | 0                | 4                               | 0.373       |
| Viral (identified)                                 | 1                | 20                              | 0.129       |
| Unidentified (presumed bacterial)                  | 9 (32.2)         | 28 (30.7)                      | 0.890       |
| Unidentified (presumed viral)                      | 19 (67.8)        | 63 (69.3)                      | 0.890       |

\(CSF\), cerebrospinal fluid; \(ME\), meningoencephalitis; \(IQR\), interquartile range; \(RT\_PCR\), reverse transcriptase polymerase chain reaction

\(p\) values in bold denote statistically significant differences \((p<0.05)\)
and admission to an ICU (OR=5.893; 95%CI=3.117–11.140), which were higher than in COVID-non-ME patients (Fig. 2).

**Discussion**

ME is a life-threatening infection associated with substantial mortality and a risk of permanent disability in survivors despite the availability of highly active antibiotics and advances in providing intensive care to critically ill patients [16]. The ME syndrome is not usually observed as a form of COVID presentation, but its incidence is higher than that observed for non-COVID patients. We found that around 0.40‰ of COVID patients in the ED had ME. While this incidence, which was determined during a 2-month period of the COVID pandemic, should be considered as low, it is more than 4-fold higher than what is usually seen in non-COVID patients. The epidemiology of ME is highly dependent on geographical factors, the development of society, and the number of preventive interventions, with an incidence of 0.6–4 cases per 100,000 adults/year in developed countries [17, 18]. In the current report, and taking into account the catchment area of the 61 EDs participating in the UMC-19-S3 study (15.2 million inhabitants), the standardized incidence of ME was 3.5 per 100,000 person/year (or 3.0 if we discount ME cases observed in patients with COVID-19). Therefore, these figures are close to those previously reported and reinforce the reliability of the data presented in the UMC-19-S3 study and suggest a direct role of SARS-CoV-2 in many of the cases of ME seen during the COVID-19 pandemic.

The profile of patients with ME in COVID patients is not different from that of ME observed in the general population in terms of demographics and comorbidity. Neck stiffness was less frequent in COVID-ME patients than in non-COVID-ME, and there was a tendency to a lower frequency of Kernig’s and Brudzinski’s signs. Within the context of a pandemic, this fact may hamper the clinical diagnosis of ME and not overlook any finding. The sensitivity of the classic triad of fever, neck stiffness, and altered mental status is low (44%), but almost all of these patients presented at least two out of the four symptoms—headache, fever, neck stiffness, and altered mental status [19]. Headache, altered mental status, and fever are present with the same frequency in COVID-ME and non-COVID-ME. All of these symptoms must make physicians aware of a possible diagnosis of ME even during the pandemic. Actually, although COVID-19 preferentially affects the

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**Table 4** Magnitude of statistically significant associations found in the unadjusted analysis

| Characteristics of meningoencephalitis in COVID patients (respect to meningoencephalitis in non-COVID patients) | Odds ratio | 95% confidence interval |
|---|---|---|
| Ground-glass lung opacities | 5.600 | 3.090–10.150 |
| Interstitial lung infiltrates | 5.369 | 2.901–9.937 |
| Dyspnea | 4.428 | 2.390–8.204 |
| Neck stiffness | 0.282 | 0.089–0.891 |

**Risk factors in COVID patients to develop meningoencephalitis (respect to COVID patients not developing meningoencephalitis)**

| Characteristics of meningoencephalitis in COVID patients (respect to meningoencephalitis in non-COVID patients) | Odds ratio | 95% confidence interval |
|---|---|---|
| Headache | 24.727 | 10.165–60.149 |
| Altered mental status | 12.864 | 6.615–25.016 |
| Neck stiffness | 12.154 | 8.410–17.564 |
| Vomiting | 3.721 | 1.353–10.234 |

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**Fig. 2** Outcomes of patients with COVID-19 and meningoencephalitis compared with controls
Limitations

This study has several limitations. First, the diagnosis of ME was based on clinical manifestations, lumbar puncture, abnormality on electroencephalography, and CT scan findings, and RT-PCR in CSF was not performed in the majority of patients. However, as explained in the “Discussion” section, a relationship between ME and SARS-CoV-2 is plausible. Second, in about half of the COVID patients with ME, SARS-CoV-2 infection was not demonstrated by RT-PCR nasopharyngeal swab, and diagnosis was based exclusively on clinical findings and the presence of the typical lung parenchymal infiltrates in chest X-ray or pulmonary CT. However, this has been the case in many countries, due to the reagent shortage experienced at the beginning of the pandemic [28, 29]. Third, as the number of cases was not large, we could not further investigate the significant relationships identified in the unadjusted analysis by using adjusted models. However, ME is a very uncommon disease, and it is very difficult to add cases quickly enough even in a national network to communicate the results during the pandemic. Additionally, a type II error cannot be ruled out due to the limited sample size of our series. Fourth, the retrospective nature of the study could have led to a loss of cases and information in the different sites. Although this information was collected from the electronic databases of the EDs, a possible selection bias cannot be ruled out, and it cannot be ensured that all the possible cases in the different hospitals were collected. Nonetheless, we believe that the results reliably reflect the epidemiology and the characteristics of ME during the COVID pandemic.

Conclusions

Despite these limitations, we conclude that the incidence of ME in COVID patients attending the ED is low, at about 0.4‰, but it is much higher than in the non-COVID population. This suggests a potential role of SARS-CoV-2 as an additional viral infection causative of ME, which could be responsible for many of the lymphocytic ME cases seen during the pandemic. In fact, the presence of the SARS-CoV-2 antigen was detected in the CSF of one of the patients included in the UMC-19-S study. Therefore, the presence of headache, altered mental status, neck stiffness, and vomiting in COVID patients should be a red flag for physicians evaluating COVID patients. The ME-COVID group had an increased risk for in-hospital mortality than non-COVID-ME.

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Declarations

Conflict of interest

The authors declare no competing interests.

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