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Original article

Neurologic manifestations associated with COVID-19: a multicentre registry

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A B S T R A C T

Objectives: To provide an overview of the spectrum, characteristics and outcomes of neurologic manifestations associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods: We conducted a single-centre retrospective study during the French coronavirus disease 2019 (COVID-19) epidemic in March–April 2020. All COVID-19 patients with de novo neurologic manifestations were eligible.

Results: We included 222 COVID-19 patients with neurologic manifestations from 46 centres in France. Median (interquartile range, IQR) age was 65 (53–72) years and 136 patients (61.3%) were male. COVID-19 was severe or critical in 102 patients (45.2%). The most common neurologic diseases were COVID-19-associated encephalopathy (67/222, 30.2%), acute ischaemic cerebrovascular syndrome (57/222, 25.7%), encephalitis (21/222, 9.5%) and Guillain-Barré syndrome (15/222, 6.8%). Neurologic manifestations appeared after the first COVID-19 symptoms with a median (IQR) delay of 6 (3–8) days in COVID-19-associated encephalopathy, 7 (5–10) days in encephalitis, 12 (7–18) days in acute ischaemic cerebrovascular syndrome and 18 (15–28) days in Guillain-Barré syndrome. Brain imaging was performed in 192 patients (86.5%), including 157 magnetic resonance imaging (70.7%). Among patients with acute ischaemic cerebrovascular syndrome, 13 (22.8%) of 57 had multiterritory ischaemic strokes, with large vessel thrombosis in 16 (28.1%) of 57. Brain magnetic resonance imaging of encephalitis patients showed heterogeneous acute nonvascular lesions in 14 (66.7%) of 21. Cerebrospinal fluid of 97 patients (43.7%) was analysed, with pleocytosis found in 18 patients (18.6%) and a positive SARS-CoV-2 PCR result in two patients with encephalitis. The median (IQR) follow-up was 24 (17–34) days with a high short-term mortality rate (28/222, 12.6%).

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Conclusions: Clinical spectrum and outcomes of neurologic manifestations associated with SARS-CoV-2 infection were broad and heterogeneous, suggesting different underlying pathogenic processes.

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Introduction

Coronavirus disease 2019 (COVID-19), the disease linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an emerging infectious disease, with the first cases reported in China in December 2019 [1,2]. The virus has continued to spread since then, and on 11 March 2020, the World Health Organization characterized COVID-19 as a pandemic. Common manifestations of the disease include respiratory tract and associated systemic manifestations, but neurologic manifestations including headaches, dizziness, anosmia, encephalopathy and stroke have been reported in cohort studies [3,4]. However, the potential pathogenesis of SARS-CoV-2 in the central nervous system remains unclear [5], and the range of neurologic disorders associated with COVID-19 is not fully defined.

The present study aimed to provide a comprehensive overview of neurologic manifestations associated with SARS-CoV-2 infection and to describe the clinical course and outcomes of COVID-19 patients with neurologic manifestations.

Methods

Study design

We conducted a retrospective single-centre observational study to collect neurologic manifestations associated with COVID-19 in 46 hospitals in France. A case report form (CRF) was sent from 16 March to 27 April 2020 to French neurologists, infectious diseases specialists and intensivists. The study complied with French Commission Nationale de l’Informatique et des Libertés (CNIL; no.

Fig. 1. Study population of coronavirus disease 2019 (COVID-19) patients with neurologic manifestations.
2217844) and ethics committee (RCB 2020-A01300-39) requirements. The local institutional review board approved the study (no. 2020-0602 COVID).

**Patients and data collection**

We included adult COVID-19 patients with any neurologic manifestations occurring 5 days before to 35 days after the first symptoms of COVID-19. A confirmed case of COVID-19 was defined as a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) real-time reverse transcriptase PCR (RT-PCR) assay result on a nasopharyngeal sample or positive SARS-CoV-2 serology. As RT-PCR analysis and serology were unavailable in some centres, some cases were considered COVID-19 if the clinical history and the chest computed tomographic (CT) scan were typical of the disease according to the referring clinicians. We excluded patients with no diagnosis of COVID-19, patients with neurologic signs that were not time related to COVID-19, patients with incomplete data on the CRF and patients with exacerbations of chronic neurologic diseases. We defined COVID-19 illness severity as mild, moderate, severe or critical according to the criteria of the US National Institutes of Health [6]. The follow-up for each patient was recorded up to the completion of the CRF by clinicians.

**Classification of neurologic manifestations**

Neurologic manifestations were identified as either related to the central nervous system (CNS) or the peripheral nervous system (PNS), then classified into categories as follows.

**Stroke**

Stroke was considered in patients with sudden neurologic deficit related to an acute vascular lesion on cerebral magnetic resonance imaging (MRI) or CT scan, in patients with transient focal deficit and normal MRI (transient ischaemic attack) or in patients with cerebral venous thrombosis.

**Encephalitis**

Encephalitis was defined as an altered mental status lasting \( \geq 24 \) hours along with one of the following criteria: white blood cell count (WBC) in cerebrospinal fluid (CSF) \(< 5/\text{mm}^3\); or presence of compatible acute lesion on brain MRI. All patients with encephalitis had CSF examination [7,8].

**Encephalopathy**

Encephalopathy was defined by an altered mental status lasting \( \geq 24 \) hours that could be associated with seizure and/or focal neurologic signs in the absence of criteria for encephalitis [8]. We identified COVID-19—associated encephalopathy (CAE) if encephalopathy could not be accounted for by another cause, such as toxic or metabolic factors, according to the reporting clinician.

**Guillain-Barré syndrome**

Guillain-Barré syndrome (GBS) was defined according to standard diagnostic criteria [9].

**Acute meningitis**

Acute meningitis was defined as meningeal syndrome (head stiffness, headache, fever) without encephalitic course and CSF WBC counts of \(< 5/\text{mm}^3\).

**Other**

Neurologic manifestations that did not meet any of these criteria were categorized as other.

**Results**

The study population comprised 259 patients, which included 222 hospitalized COVID-19 patients with neurologic manifestations from 46 centres in all regions of continental France and overseas (Fig. 1, Supplementary Appendix S2). Participating physicians were neurologists (146/222, 65.8%), infectious diseases or internal medicine specialists (43/222, 19.4%), intensivists (14/222, 6.3%) or other specialists (19/222, 8.6%). The prevalence of neurologic manifestations among COVID-19 patients was estimated in one centre to be 8.8%; 43 patients with neurologic manifestations were reported from a total of 490 patients hospitalized with COVID-19.

**Table 1**

General characteristics of 222 COVID-19 patients with neurologic manifestations

| Characteristic                        | Value                  |
|---------------------------------------|------------------------|
| Age (years), median (IQR)             | 65 (53–72)             |
| Male                                  | 136 (61.3)             |
| Neurologic comorbidities              | 47 (21.2)              |
| Prior stroke                          | 20 (9.0)               |
| Neurodegenerative disease             | 17 (7.7)               |
| Epilepsy                              | 5 (2.3)                |
| Other                                 | 5 (2.3)                |
| Diagnosis of COVID-19                 |                        |
| Positive SARS-CoV-2 nasopharyngeal PCR| 192 (86.5)             |
| Positive SARS-CoV-2 serology          | 4 (1.8)                |
| Typical clinical course and chest CT  | 26 (11.7)              |
| Severity of COVID-19                  |                        |
| Mild                                  | 55 (24.8)              |
| Moderate                              | 65 (29.3)              |
| Severe                                | 46 (20.7)              |
| Critical                              | 56 (25.2)              |
| Occurrence of neurologic manifestations|                       |
| Neurologic manifestations occurring as| 45 (20.3)              |
| first symptoms                        |                        |
| Neurologic manifestation occurring after| 141 (63.5)             |
| COVID-19 symptoms                     |                        |
| Time (days) between first symptoms and| 7 (1–12)               |
| neurologic manifestation, median (IQR)|                        |
| Neurologic manifestation after withholding| 36 (16.2)              |
| sedation in ICU                       |                        |
| Neurologic symptoms                   |                        |
| Altered mental status                 | 117 (52.4)             |
| Focal central neurologic symptoms     | 97 (43.7)              |
| Peripheral limb weakness              | 26 (11.7)              |
| Headache                              | 24 (10.8)              |
| Seizure                               | 21 (9.5)               |
| Cranial neuropathy                    | 10 (4.5)               |
| Movement disorder                     | 8 (3.6)                |
| Anosmia                               | 7 (3.2)                |
| Dizziness                             | 5 (2.3)                |
| Ageusia                               | 4 (1.8)                |
| Neurologic assessment                 | 205 (92.3)             |
| Brain imaging                         | 192 (86.5)             |
| Brain MRI                             | 157 (70.7)             |
| Brain CT scan                         | 35 (15.8)              |
| Presence of acute lesion, n/N (%)     | 85/192 (44.3)          |
| Spine MRI                             | 6 (2.7)                |
| Cerebrospinal fluid examination       | 97 (43.7)              |
| WBC count >5/mm\(^3\), n/N (%)        | 18/97 (18.6)           |
| SARS-CoV-2 PCR in cerebrospinal fluid | 75 (33.8)              |
| Positive, n/N (%)                     | 27/5 (2.7)             |
| Electroencephalogram                   | 74 (33.3)              |
| Electroneuromography                  | 19 (8.6)               |
| Follow-up (days), median (IQR)        | 24 (17–34)             |
| Death                                 | 28 (12.6)              |
| Acute respiratory distress syndrome    | 17 (7.7)               |
| Stroke                                | 5 (2.3)                |
| Other                                 | 6 (2.7)                |

Data are presented as n (%) unless otherwise indicated. COVID-19, coronavirus disease 2019; CT, computed tomography; ICU, intensive care unit; IQR, interquartile range; MRI, magnetic resonance imaging; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell. 

* According to National Institute of Health guidelines.
General characteristics of COVID-19 patients with neurologic manifestations

Median (interquartile range, IQR) age was 65 (53–72) years and 136 patients (61.3%) were male (Table 1). Forty-seven patients (21.2%) had a neurologic history, mostly prior stroke (20, 9.0%) and neurodegenerative disease (17, 7.7%). The diagnosis of COVID-19 was confirmed by a positive SARS-CoV-2 PCR result in 192 patients (86.5%) and by serology in four patients (1.8%). Twenty-six patients (11.7%) had a diagnosis that was based on a typical clinical course and imaging. COVID-19 severity was severe or critical in 102 patients (45.2%). The most common neurologic symptom was altered mental status (117, 52.4%). Neurologic assessment mostly included brain MRI (157, 70.7%) and CSF examination (97, 43.7%). SARS-CoV-2 PCR was performed on CSF samples in 75 patients (33.8%) and was negative in 73 (97.3%) of them. The median (IQR) follow-up was 24 (17–34) days. Twenty-eight patients (12.6%) died, mostly following acute respiratory distress syndrome (n = 17, 7.7%) or stroke (2.3%).

Clinical spectrum of neurologic manifestations associated with SARS-CoV-2 infection

CNS manifestations

One hundred eighty-nine patients (85.1%) had CNS manifestations, mostly encephalopathy (85/222, 38.3%), stroke (63/222, 28.4%) and encephalitis (21/222, 9.5%) (Fig. 1). The distribution of stroke was as follows: acute ischaemic cerebrovascular syndromes (AICS, 57/63) including 52 acute ischaemic strokes and stroke was as follows: acute ischaemic cerebrovascular syndromes, mostly following acute respiratory distress syndrome (21.2%) had a neurologic history, mostly prior stroke (20, 9.0%) and encephalitis (21/222, 9.5%) (Fig. 1). The distribution of neurologic manifestations was CAE (67/222, 30%), GBS (5/222, 2.3%), stroke (63/222, 28.4%) and encephalitis (21/222, 9.5%) (Table 2). The remaining patients exhibited neurologic manifestations several days after the first COVID-19 symptoms, with a median (IQR) delay of 6 (3–8) days and 7 (5–10) days respectively in CAE and encephalitis patients, and 12 days (IQR 7–18) in AICS and 18 days (IQR 15–28) in GBS.

Acute ischaemic cerebral syndrome

Median (IQR) age was 65 (55–78) years. Eight patients (14.0%) had a history of stroke and 43 (75.4%) of 57 had known cardiovascular risk factors: 34 had hypertension, 15 had diabetes, 13 had dyslipidaemia, seven were obese and five were active smokers. Large vessel infarct (Fig. 2(L–O)) was observed in 46 (88.4%) of 57 patients, with persisting thrombosis noted in 16 patients (16.1%). Thirteen patients (22.8%) experienced multiterritory ischaemic stroke. AICS was cryptogenic (ischaemic stroke for which no probable cause was found despite thorough diagnostic evaluation) in 38 (66.7%) of 57 patients. The mortality rate was 15.8%.

Encephalitis

Median (IQR) age was 67 (51–70) years. More than half of the patients (12/21, 57.1%) exhibited focal neurologic deficit in addition to altered mental status, with predominant cerebellar ataxia and pyramidal syndrome. Six patients (28.6%) also had movement disorders, mostly tremor and myoclonus. Brain MRI was abnormal in 14 (66.7%) of 21 patients with imaging compatible with encephalitis (Table 3, Fig. 2(A–G)). CSF examination demonstrated lymphocytic pleocytosis, with WBC count from 6 to 77/mm3 in 14 (66.7%) of 21 patients. SARS-CoV-2 PCR results of CSF testing were positive in two patients, both of whom had critical COVID-19 illness. Electroencephalogram was abnormal in 14 (93.3%) of the 15 patients so assessed (Table 3). Ten patients (47.6%) fully recovered, three of whom received corticosteroids. The mortality rate was 4.8%.

COVID-19–associated encephalopathy

Median (IQR) age was 68 (61–75) years and 20 (29.9%) of 67 had neurodegenerative disease. The majority of CAE patients experienced severe to critical COVID-19 (46/67, 68.7%). Neuroimaging was unremarkable except for six patients (9%) with acute small cerebral infarcts unrelated to clinical symptoms (Fig. 2(H–K)) and one with a typical reversible lesion of the splenium of corpus callosum. Thirty-four patients (50.7%) recovered spontaneously. Two patients received corticosteroids with partial improvement. The mortality rate was 14.9%.

Guillain-Barré syndrome

Median (IQR) age was 59 (53–65) years and ten (66.7%) of 15 had mild or moderate COVID-19. Fourteen patients had CSF examinations, that demonstrated isolated elevated protein levels in eight (57.1%) of them, ranging from 0.49 to 2.36 g/L. Negative SARS-CoV-2 PCR results were obtained in nine patients tested. Electroneuromyography was performed in 14 patients and was suggestive of demyelination in 13 (92.9%) of them.

Most patients with GBS, 14 (93.3%) of 15, were treated with intravenous immunoglobulin. Two required mechanical ventilation. There was no mortality during follow-up.

Discussion

Our results highlight the broad spectrum of neurologic manifestations associated with SARS-CoV-2 infection: the majority of neurologic manifestations were CAE (67/222, 30%), AICS (57/222, 26%), encephalitis (21/222, 10%) or GBS (15/222, 7%). Neurologic manifestations appeared after the first COVID-19 symptoms after a median delay of 6 days in CAE, 7 days in encephalitis, 12 days in AICS and 18 days in GBS. With a
Fig. 2. Brain MRI from patients with encephalitis or atypical strokes. (A–D) Patient 1, a 56-year-old woman with encephalitis, experienced headache, confusion, facial palsy, ophthalmoparesis, refractory status epilepticus and pleocytosis. SARS-CoV-2 PCR results were positive in respiratory sample but negative in CSF. Bilateral basal ganglia and thalami exhibited FLAIR hyperintensity (A), with small subcortical white matter FLAIR hyperintensities (B) visible in diffusion (C) with normal ADC map (D). (E) Patient 2, a 58-year-old man with encephalitis, was found to be SARS-CoV-2 PCR positive in nasopharyngeal swab sample and negative in CSF sample. Pleocytosis and left mesiotemporal and temporopolar hyperintensity were evident on axial FLAIR (E). (F, G) Patient 3, a 49-year-old man with encephalitis, experienced psychomotor agitation and inattention after withdrawal of
median delay of follow-up of 24 days, our registry found a high rate of short-term mortality in COVID-19 patients with CAE and AICS of around 15% (19/124).

Altered mental status was reported in 52% of patients in our registry. Several cohorts of hospitalized patients with COVID-19 have shown a significant proportion of impaired consciousness, ranging from 7.5% to 20% [1,3,4,10]. Encephalitis represented up to 10% of patients in our registry; more than half had focal neurologic deficit. Ellul et al. [8] suggested case definitions for neurologic associations of COVID-19. COVID-19 encephalitis is considered confirmed in a patient with encephalitis (as defined by Venkatesan et al. [7]) and specific intrathecal antibody or SARS-CoV-2 found in the CSF or the brain (PCR or culture). COVID-19 encephalitis is probable if SARS-CoV-2 is found in a respiratory sample. Following these definitions, we found two confirmed COVID-19 encephalitis and 19 probable COVID-19 encephalitis cases. Brain MRI results were highly heterogeneous, consistent with the published cases of encephalitis: white matter lesion and/or basal ganglia and thalamic involvement suggestive of acute disseminated encephalomyelitis [11] or acute necrotizing encephalopathy [12–14], other nonspecific diffuse involvement of white matter [15,16], mesiotemporal lesions [10,17] with possible frontoinsular extension, leptomeningeal abnormalities [4] and brainstem lesions [18]. Only two patients in our registry had a positive SARS-CoV-2 PCR result from a CSF sample. Two other encephalitis patients with positive SARS-CoV-2 PCR results from CSF testing have been reported [11,17].

In our series, the short-term outcome was generally favourable without any specific treatment, suggesting a parainfectious

### Table 2
Baseline and clinical characteristics of COVID-19 patients with acute ischaemic cerebrovascular syndrome, encephalopathy, encephalitis and GBS

| Characteristic | Acute ischaemic cerebrovascular syndrome (n = 57) | Encephalitis (n = 21) | COVID-19–associated encephalopathy (n = 67) | GBS (n = 15) |
|---------------|---------------------------------|-------------------|---------------------------------|-------------|
| Age (years), median (IQR) | 65 (55–78) | 67 (51–70) | 68 (61–75) | 59 (53–65) |
| Male | 34 (59.6) | 15 (71.4) | 41 (60.3) | 13 (86.7) |
| Medical history | | | | |
| Prior stroke | 8 (14.0) | 0 | 4 (6.0) | 1 (6.7) |
| Neurodegenerative disease | 1 (1.8) | 1 (4.8) | 20 (29.9) | 0 |
| Vascular comorbidities* | 43 (75.4) | NA | NA | NA |
| Severity of COVID-19 | | | | |
| Mild | 21 (36.8) | 4 (19) | 6 (9.0) | 7 (46.7) |
| Moderate | 16 (28.1) | 7 (33.3) | 16 (23.9) | 3 (20.0) |
| Severe | 13 (22.8) | 3 (14.3) | 16 (23.9) | 1 (6.7) |
| Critical | 7 (12.3) | 7 (33.3) | 29 (43.3) | 4 (26.7) |
| Neurologic manifestations occurrence | | | | |
| Neurologic manifestations occurring as first symptoms | 14 (24.6) | 1 (4.8) | 15 (22.4) | 0 |
| Neurologic manifestation occurring after first COVID-19 symptoms | 40 (70.2) | 14 (66.7) | 32 (47.8) | 12 (80.0) |
| Time between first symptoms and neurologic manifestation, median (IQR), day | 12 (7–18) | 7 (5–10) | 6 (3–8) | 18 (15–28) |
| Neurologic manifestation after withholding sedation in ICU | 3 (5.3) | 6 (28.6) | 20 (29.9) | 3 (20.0) |
| Neurologic symptoms | | | | |
| Headache | 2 (3.5) | 3 (14.3) | 6 (9.0) | 0 |
| Altered mental status | 8 (14.0) | 21 (100) | 67 (100) | 3 (20.0) |
| Seizure | 1 (1.8) | 2 (9.5) | 7 (10.4) | 0 |
| Focal central neurologic symptoms | 56 (98.2) | 12 (57.1) | 13 (19.4) | 2 (13.3) |
| Motor or sensitive deficit | 42 (73.7) | 2 (9.5) | 1 (1.5) | 1 (6.7) |
| Cerebellar ataxia | 6 (10.5) | 6 (28.6) | 9 (13.4) | 0 |
| Pyramidal syndrome | NA | 6 (28.6) | 4 (6.0) | 0 |
| Central oculomotor syndrome | 6 (10.5) | 1 (4.8) | 1 (1.5) | 1 (6.7) |
| Movement disorder | 0 | 6 (28.6) | 3 (4.5) | 1 (6.7) |
| Peripheral limb weakness | 1 (1.8) | 2 (9.5) | 7 (10.4) | 11 (73.3) |
| Cranial neuropathy | 0 | 1 (4.8) | 2 (3.0) | 4 (26.7) |
| Follow-up (days), median (IQR) | 24 (16–32) | 21 (18–29) | 28 (19–37) | 18 (14–29) |
| Resolution of neurologic symptoms | 21 (36.8) | 10 (47.6) | 34 (50.7) | 1 (6.7) |
| Death | 9 (15.8) | 1 (4.8) | 10 (14.9) | 0 |

Data are presented as n (%) unless otherwise indicated. COVID-19, coronavirus disease 2019; GBS, Guillain-Barré syndrome; ICU, intensive care unit; IQR, interquartile range; NA, not applicable.

* Vascular comorbidities were only collected for patients with stroke. Data included hypertension, diabetes, obesity and cardiovascular diseases.
mechanism rather than direct neuropathogenicity of SARS-CoV-2. In an autopsy study of six COVID-19 patients, von Weyhern et al. [19] highlighted the presence of lymphocytic panencephalitis and meningitis. Another study documented the presence of SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell count.

In an autopsy study of six COVID-19 patients, von Weyhern et al. [19] highlighted the presence of lymphocytic panencephalitis and meningitis. Another study documented the presence of SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell count.

Table 3

| Characteristic | Acute ischaemic cerebrovascular syndrome (n = 57) | Encephalitis (n = 21) | Encephalopathy (n = 67) | GBS (n = 15) |
|---------------|-----------------------------------------------|----------------------|------------------------|--------------|
| Brain imaging | 57 (100)                                      | 21 (100)             | 57 (85.1)              | 5 (33.3)     |
| CT scan       | 9 (15.8)                                      | 0                    | 12 (17.9)              | 0            |
| MRI           | 48 (84.2)                                     | 21 (100)             | 45 (67.2)              | 2 (13.3)     |
| Acute ischaemic lesion | 52 (91.7)                                | 2 (9.5)               | 6 (9)                  | 2 (13.3)     |
| Unifocal ischaemic lesion | 39 (68.4)                                | 1 (4.8)               | 5 (7.5)                | 1 (6.7)      |
| Multifocal ischaemic lesions | 13 (22.8)                                 | 1 (4.8)               | 0                      | 1 (6.7)      |
| Large vessel infarct | 46 (84.4)                                  | 0                    | 0                      | 1 (6.7)      |
| Small vessel infarct | 6 (11.5)                                    | 2 (9.5)               | 6 (9)                  | 1 (6.7)      |
| Microhemorrhages | 2 (9.5)                                      | 2 (9.5)               | 3 (4.5)                | 0            |
| Other lesion  | 14 (66.7)                                    | 1 (4.8)               | 1 (1.5)                | 0            |
| Spine MRI     | 0                                            | 0                    | 2 (3)                  | 3 (20)       |
| Any lesion    | —                                            | —                    | 0                      | 0            |
| Cerebrospinal fluid examination | 3 (5.2)                                   | 21 (100)             | 36 (53.7)              | 14 (93.3)    |
| WBC count >5/mm³ | —                                          | 14 (66.7)             | 0                      | 1 (6.7)      |
| Proteins >0.45 g/L | —                                             | 12 (57.1)             | 8 (11.9)               | 8 (53.3)     |
| Isolated elevated proteins | —                                           | 4 (19.0)              | 8 (11.9)               | 8 (53.3)     |
| Positive SARS-CoV-2 PCR | —                                    | 2 (9.5)               | 0                      | 0            |
| Electroencephalogram | 4 (7.0)                                    | 15 (71.4)             | 32 (47.8)              | 2 (14.3)     |
| Diffuse slowing | 3 (5.3)                                      | 9 (42.9)              | 17 (25.4)              | 1 (6.7)      |
| Anterior slowing | 3 (14.3)                                     | 4 (19)                | 8 (11.9)               | 0            |
| Focal lateralized slowing and/or paroxysm | 1 (1.8)                       | 1 (4.8)               | 3 (4.5)                | 0            |
| Periodic pattern | 1 (1.8)                                     | 1 (4.8)               | 1 (1.5)                | 0            |
| Status epilepticus | 1 (1.8)                                    | 1 (4.8)               | 1 (1.5)                | 0            |
| Electroneurography | 1 (1.8)                                    | 1 (4.8)               | 3 (4.5)                | 14 (93.3)    |
| Abnormal findings | 1 (1.8)                                     | 1 (4.8)               | 3 (4.5)                | 13 (86.7)    |
| Axonal injury  | 1 (1.8)                                      | 1 (4.8)               | 1 (1.5)                | 0            |
| Demyelination  | 0                                            | 0                    | 2 (3)                  | 13 (86.7)    |

Data are presented as n (%). COVID-19, coronavirus disease 2019; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; GBS, Guillain-Barré syndrome; MRI, magnetic resonance imaging; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell count.

* Among 46 patients with large vessel infarct, 16 had a persisting thrombosis located in internal carotid artery (n = 9) and/or proximal segment of middle cerebral artery (n = 6) or in basilar artery (n = 1).

* Basal ganglia FLAIR hyperintensity (n = 3), acute diffuse hemispheric white matter lesions (n = 2), FLAIR hyperintensity of genu of corpus callosum (n = 1), mesiotemporal FLAIR hyperintensity (n = 3) with frontoinsular extension in 2, brainstem and cerebellar peduncular FLAIR hyperintensity (n = 2), cranial nerve FLAIR hyperintensity (n = 1), focal leptomeningeal FLAIR hyperintensity (n = 2).

* Lesion in splenium of corpus callosum typical of mild encephalopathy with reversible splenial lesion syndrome.

multiterritory involvement [31], undetermined aetiology [32] and high mortality rate [32]. Several cases of GBS are currently reported in the literature [33–38], and one study has demonstrated an increased incidence of GBS during the COVID-19 epidemic compared to the three previous years [39]. GBS cases reported in this study can be considered to be probably associated with COVID-19, as defined by Ellul et al. [8].

Our study has several limitations. Firstly, this is a retrospective registry analysis, with all the reporting biases inherent in this mode, which means that the different proportions of neurologic manifestations should be interpreted with caution. Hospitals participated in the study on a voluntary basis, and our sample is probably not representative of all health facilities in France. However, our objective was to present a panel of neurologic manifestations associated with SARS-CoV-2 and their clinical description, not estimate the proportion of neurologic diseases among the entire population of COVID-19 patients. We think that with 46 participating centres including general hospitals as well as specialized neurology centres, we have captured a large panel of COVID-19 neurologic manifestations. Secondly, we only included hospitalized patients, so neurologic symptoms or manifestations associated with milder ambulatory forms of COVID-19 are probably underreported. This could explain why a low proportion of patients with dizziness or anosmia were found in this study. Thirdly, this registry focused on the acute phase of COVID-19 with a limited follow-up duration; we did not study long-term symptoms, including neurologic complaints, described in a variable proportion of patients with long COVID-19 [40]. Fourthly, the data are entirely published articles: high prevalence of large-vessel stroke [30,31],
descriptive and are based on the report at a definite time period during the French outbreak. We used a deliberately simplified CRF, given the exceptional workload shouldered by the medical teams; there was no exhaustive collection of medical history other than neurologic comorbidities and vascular comorbidities for AICS; nor did we analyse biological parameters. Fifthly, some neurologic manifestations that we report here may not be specific to SARS-CoV-2 infection, such as critical illness neuropathy or Tapia syndrome. Further studies are needed to study the direct or indirect role of SARS-CoV-2 infection in the different neurologic manifestations exhibited by patients with COVID-19.

Conclusions

Our study highlights the broad spectrum of neurologic manifestations associated with SARS-CoV-2 infection, which is probably related to different pathogenic pathways. Although encephalopathies were the most frequently reported manifestations, possibly linked to sepsis and cytokine storm, encephalitis was described in 10% of cases. A large majority of SARS-CoV-2 PCR results of CSF (73/75, 97.3%) were negative, and the short-term outcome of patients with encephalitis was generally favourable. Ischaemic strokes were also frequently reported, as was GBS, which occurred later in the course of the disease (18 days, compared to 7 days for encephalitis and 12 days for stroke). Further studies are needed to understand the physiopathology of neurologic manifestations in COVID-19 patients.

Transparency declaration

All authors report no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.11.005.

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