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Clinical description of the broad range of neurological presentations of COVID-19: a retrospective case series

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Abstract

Background

Neurological disorders associated with SARS-CoV-2 infection represent a clinical challenge because they encompass a broad neurological spectrum and may occur before the diagnosis of COVID-19.

Methods

In this monocentric retrospective case series, medical records from patients with acute neurological disorders associated with SARS-CoV-2 infection from medicine departments of an academic center in Paris area were collected between March 15th and May 15th 2020. Diagnosis of SARS-CoV-2 was ascertained through specific RT-PCR in nasopharyngeal swabs or based on circulating serum IgG antibodies.

Results

Twenty-six patients diagnosed with SARS-CoV-2 infection presented with neurological disorders: encephalitis (N=8), encephalopathy (N=6), cerebrovascular events (ischemic strokes N=4 and vein thromboses N=2), other central nervous system (CNS) disorders (N=4), and Guillain-Barré syndrome (N=2). The diagnosis of SARS-CoV-2 was delayed on average 1.6 days after the onset of neurological disorder, especially in case of encephalitis 3.9 days, encephalopathy 1.0 day, and cerebrovascular event 2.7 days.

Conclusions

Our study confirms that COVID-19 can yield a broad spectrum of neurological disorders. Because neurological presentations of COVID-19 often occur a few days before the diagnosis of SARS-COV-2 infection, clinicians should take preventive measures such as patient isolation and masks for any new admission to avoid nosocomial infections. Anti-SARS-CoV2 antibody detection in RT-PCR SARS

CoV-2 negative suspected cases is useful to confirm *a posteriori* the diagnosis of atypical COVID-19 presentations.

Keywords : Amyotrophic Lateral Sclerosis; diaphragmatic ultrasonography; pulmonary function tests; phrenic nerve conduction

Introduction

Neurological disorders observed in the course of the Coronavirus 2019 disease (COVID-19) represent a challenge for clinicians. Some of these neurological disorders have been reported in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia and acute respiratory distress syndrome (ARDS) in intensive care units (ICU).(1) Those patients have a poorer prognosis compared to patients without neurological symptoms.(2) However, reports suggest that various neurological disorders may also occur in patients with SARS-CoV-2 infection but no clinical evidence of respiratory dysfunction.(3–6) Among these neurological disorders associated with SARS-CoV-2 infection, encephalitis, encephalopathy, cerebrovascular event, and Guillain-Barré syndrome are the most frequent.(7–10) Anosmia and ageusia often reported in COVID-19 patients could be of neurological origin or related to an epithelial disorder of the nasopharynx.(11,12) Anosognosia for hypoxia has been observed in patients with SARS-CoV-2 pneumonia and debate is still ongoing to decide whether this syndrome relates to a pulmonary shunt effect or to a central nervous system (CNS) involvement.(13)

According to our experience of neurological presentations of COVID-19 during the first wave that occurred in France between March and May 2020, one major caveat for clinicians was the delay between the onset of the neurological disorder and the actual diagnosis of COVID-19. Before the COVID-19 diagnosis and without appropriate protection measures, clinicians could expose the hospital community to a nosocomial risk due to an unknown SARS-CoV-2 infection associated with the neurological disorder. The diagnosis of this infection commonly relies on reverse transcriptase – polymerase chain reaction (RT-PCR) specific for SARS-CoV-2 in nasopharyngeal swabs but during the first wave of the outbreak the result of this test was usually available after up to one day and its sensitivity variable. Diagnostic sensitivity of RT-PCR for SARS-CoV-2 has been found to be the highest at the initial phase of the disease, especially in patients with anosmia, fever, or typical SARS-CoV-2 pneumonia, but dramatically lower from one week after the onset of the infection or in atypical presentations of the disease.(14,15) Serology testing for immunoglobulin G against SARS-CoV-2 is another useful method for ascertaining the diagnosis of COVID-19, but the delayed immune response

makes this test usually positive 10 to 15 days after disease onset.(15) Acknowledging this diagnosis challenge, chest CT-scan exam for looking at typical signs of SARS-CoV-2 pneumonia has been a surrogate criterion for the diagnosis of COVID-19 during the first months of the outbreak.(16,17)

Here, we have reviewed all cases of neurological disorders observed in patients with proven COVID-19 in medicine departments of a French public faculty hospital in Paris area. We did not include the patients with ARDS still hospitalized in ICU in this retrospective case series. We compared the clinical and biological features of the different neurological disorders associated with SARS-CoV-2 infection. In addition, we examined the delay between the onset of the neurological symptoms and the diagnosis of the SARS-CoV-2 infection.

Methods

Retrospective data from patients hospitalized in an academic center in Paris area between March 15th 2020 and May 15th 2020 were screened for neurological disorders and COVID-19. Cases were identified in medicine departments (neurology, emergency care, nephrology, cardiology, gerontology, infectious diseases), excluding patients hospitalized in ICU. We also included patients in medicine departments with a past hospitalization in ICU who did not require artificial respiratory assistance. We applied a two-criteria diagnostic algorithm for ascertaining neurological presentations of COVID-19: 1) a confirmed SARS-CoV-2 infection(18) and 2) acute or subacute neurological disorder occurring during or within four weeks after the SARS-CoV-2 infection.

The confirmed diagnosis of COVID-19 was established using either a positive RT-PCR for SARS-CoV-2 in nasopharyngeal swabs or by the presence of serum IgG anti-SARS-COV2 (Architect ABBOTT). The date onset of SARS-CoV-2 infection corresponded to the first symptom, whether neurological or not, attributable to COVID-19. The date of neurological symptoms was collected according to medical records. We also collected the date when the diagnosis of COVID-19 was first available based on positive RT-PCR for SARS-CoV-2 or positive serology, and the date of chest CT-scan when showing typical symptoms of SARS-CoV-2 pneumonia. A typical SARS-CoV-2

pneumonia was diagnosed when chest CT-scan showed abnormalities including ground-glass opacities, linear densities, reticulations, crazy paving and predominant peripheral distribution.(17,19)

We followed the recently proposed case definitions for the associated of COVID-19 with neurological disease.(9) Encephalitis was diagnosed in patients with altered consciousness or delirium lasting for more than 24 hours and evidence for focal neurological involvement (clinical, electroencephalogram (EEG) or brain imaging) or for CSF inflammation (> 5 cells/mm³). (20) Encephalopathy was diagnosed in patients with altered consciousness or delirium, no focal neurological symptoms and without evidence of CNS inflammation (CSF testing or brain imaging). Cerebrovascular events (acute ischemic stroke, hemorrhage or central vein thrombosis) were diagnosed with either injected brain CT-scan or brain MRI. Guillain-Barré syndromes (GBS) were diagnosed on the basis of electrophysiology results associated with clinic and CSF testing.

This study (N° NI20200408HLJ) has been approved on April 10th 2020 by the institutional review board of Henri Mondor hospital.

Anonymized data are available upon request to the corresponding author.

Results

Applying our diagnostic algorithm, we identified twenty-six neurological cases of COVID-19: eight with encephalitis, six with encephalopathy, six with cerebrovascular event (four ischemic strokes and two vein thromboses), four with other CNS disorders (posterior reversible encephalopathy, tonic-clonic seizure and pachymeningitis, demyelinating white matter abnormalities, migraine with associated aura) and two with GBS, a peripheral nervous system (PNS) disorder. Three patients had pre-existing cognitive impairment. For all patients with the exception of one patient with history of stroke, these neurological disorders appeared for the first time in the context of their COVID-19.

Neurological presentations of COVID-19

Table 1 summarizes demographics, comorbidities and clinic-biologic findings in patients with neurological presentation of COVID-19. The age range was large, from 16 to 86 years, with a majority of male (73.1%). The most common comorbidity was hypertension (38.5%). The total stay in hospitalization lasted 14.3 days on average and three patients (11.5%) died from the COVID-19 infection. Only four patients (15.4%) had been previously hospitalized in ICU for ARDS. Accordingly, at time of neurological examination, the average blood saturation in oxygen was 92.7%.

Encephalitis

The eight patients with encephalitis(9) showed a large spectrum of neuropsychiatric symptoms, including paranoid thinking (e.g. feeling that family members or nurses intended to hurt the patient) or spatial delusion (e.g. belief of being on holiday by the sea despite normal temporal orientation) (62.5%), delirium (50%) and agitation (50%). The Montreal Cognitive Assessment(21) (MoCA) showed impaired cognitive performance (average score 18.4/30) related to a dysexecutive syndrome in the 5 tested patients. Other symptoms were less frequent and included altered consciousness (25%), visual hallucinations including animals (spiders, birds), persons or demons (25%), anxiety (25%) and cerebellar ataxia (25%). The average stay in hospital was 20.8 days \pm 14.0 and none of these cases died. These patients did not suffer from severe respiratory dysfunction at time of neurological examination, as their blood oxygen saturation was 91.5% on average. Biological tests showed that this group had a severe inflammatory syndrome (elevated C-reactive protein, fibrinogen and ferritin). Neurological symptoms of encephalitis faded when the inflammatory syndrome disappeared. Importantly, patients with encephalitis showed frequent renal failure (but only one patient had a previously known renal dysfunction), mild liver dysfunction, and frequent rhabdomyolysis. Cerebrospinal fluid (CSF) was analyzed in seven cases: cell count was 18.8/mm³ on average (three patients had more than 5 cells/mm³), with normal glucose level (3.2 mmol/L) and mildly elevated protein concentrations (0.6 g/L). The RT-PCR for SARS-CoV-2 was negative in CSF for all tested patients. Brain magnetic resonance imaging (MRI) was normal in all patients and asymmetric slow waves on EEG were found in two out of the four tested patients.

Encephalopathy

The six patients with encephalopathy were older men. All showed symptoms of delirium (100%), while episodes of altered consciousness were observed in four of them (66.7%) and agitation in two patients (33.3%). One patient had been previously admitted in ICU for ARDS. At time of neurological examination, their mean blood oxygen saturation was 90.2% in ambient air. The duration of hospital stay was shorter than for encephalitis cases, but two patients (33.3%) died in this group due to SARS-CoV-2 pneumonia complications. As in patients with encephalitis, a severe inflammatory syndrome was observed (elevated C-reactive protein, fibrinogen and ferritin), which improved concomitantly to neurological recovery in patients with favorable outcome. Lymphopenia was found in these patients. Mild kidney, liver and muscle dysfunction were present. CSF cell count and brain imaging were normal in the tested patients. EEG did not show focal abnormalities or asymmetries.

Cerebrovascular events

Four patients had ischemic strokes and two central vein thromboses. Two patients with ischemic stroke were younger than forty years. Half of these patients showed symptoms of delirium and altered consciousness at entrance suggesting associated encephalopathy. The four patients with stroke had a mean National Institutes of Health Stroke Scale score (NIHSS) of 15.5 (aphasia, hemiplegia, hemineglect and hemianopsia). These four patients had occlusion of intracerebral arteries: three patients with left or right middle cerebral artery occlusion, one with right posterior cerebral artery occlusion. Three patients with ischemic stroke were treated with intra-venous thrombolysis and thrombectomy. Another patient recovering from ARDS managed in ICU showed symptoms of delirium for three weeks before presenting with dysarthria and cephalalgia revealing a left frontal superior cortical vein thrombosis on brain MRI. A last patient presented with altered consciousness, cephalalgia and fever. His injected brain CT-scan showed extended central vein thromboses (superior and inferior sagittal sinuses, straight sinus, both transverse sinuses, proximal portion of internal cerebral vein and right internal jugular vein), left temporal infarct and diffuse edema. Both patients with central vein thromboses were treated with heparin. This group of six patients showed very few

cardio-vascular risk factors: none of them had hypertension, diabetes, dyslipidemia, or obesity, and only two reported tobacco use. One patient was suspected to suffer from a SARS-CoV-2 associated myocarditis. One patient had a previous history of silent stroke as revealed by brain MRI. Another died from SARS-CoV-2 pneumonia complications. All patients had a mild inflammatory syndrome but no kidney, liver or muscle dysfunction. Two patients were found with lupus anticoagulant antibodies and another with IgM anticardiolipin antibodies. CSF analysis showed mild signs of inflammation in the three tested patients. Their mean hospital stay lasted $14.3 \text{ days} \pm 11.5$.

Other CNS disorders

This group includes heterogeneous neurological disorders in younger patients. Two patients presented with first tonic-clonic seizure revealing a pachymeningitis with subdural hemorrhage in one patient and a posterior reversible encephalopathy syndrome (PRES) in the other (described in reference (22)). Another patient showed transient visual and language disorders associated with cephalalgia, which were diagnosed as migraine with aura. The last patient had an asymmetric cerebellar syndrome revealing demyelinating white matter abnormalities including gadolinium-enhanced cerebellar lesion on brain MRI. Neurological symptoms were mild in this group, with favorable outcome. No patient had a respiratory dysfunction. A mild inflammatory syndrome was noted in the patient with PRES. Hospital stay lasted $9.0 \text{ days} \pm 9.1$.

Guillain-Barré syndrome

Two patients were diagnosed with Guillain-Barré syndrome (GBS). One patient had mild motor and sensitive symptoms contemporary to a mild SARS-CoV-2 infection with asthenia, diarrhea and positive contact with colleagues with SARS-CoV-2 infection. The second patient presented with facial diplegia and progressive motor and sensitive disturbances three weeks after a mild COVID-19 infection with anosmia. Both patients showed accentuated brisk deep tendon reflexes at onset of their disease but follow-up showed a diminution of reflexes responses after few days. One patient had a typical albumin-cytologic dissociation in CSF while the other had normal CSF exam. None showed

any inflammatory syndrome. Both patients showed typical pattern of GBS on nerve conduction studies: altered or absent F waves, increased distal motor latencies, reduced motor conduction velocities with conduction blocks, and reduced amplitude of distal sensory nerve action potentials predominantly at the upper limbs. Overall, clinical deficits remained mild to moderate and only one patient required hospitalization and intra-venous immunoglobulins perfusion. Both patients were significantly improved one month later, with only mild clinical and electrophysiological sequelae.

Challenges in diagnosing neurological presentations of COVID-19

Table 2 describes clinical symptoms and tests that allowed the diagnosis of a SARS-CoV-2 infection in these patients. As a whole, 72% of patients with neurological presentation of COVID-19 were diagnosed by evidencing a positive RT-PCR for SARS-CoV-2 in nasopharyngeal swabs. The 28% remaining patients were identified using EIA IgG specific antibodies. SARS-CoV-2 pneumonia was confirmed in 19 out of 22 (86.4%) of patients with neurological presentation of COVID-19 in whom chest-CT scan was performed. The average delay between infection onset and neurological symptoms onset was 8.2 days \pm 8.8. Importantly, the diagnostic of COVID-19 was confirmed 1.6 day on average \pm 5.4 after the onset of the neurological condition with large variations according to the patients. A minority of these patients reported a contact with a person affected by COVID-19 or an anosmia/ageusia (34.6 % and 38.5 % respectively).

Encephalitis vs. encephalopathy

In our series, patients with COVID-19 encephalitis were challenging to diagnose because RT-PCR for SARS-CoV-2 was often negative (50%) which explained the important mean delay (3.9 days \pm 4) between the onset of the encephalitis and the biological diagnosis of the infection. Although frequently found, an associated SARS-COV-2 pneumonia was not systematic. Thus, a normal chest CT-scan could not rule out a COVID-19 encephalitis. Conversely, patients with COVID-19 encephalopathy were easier to diagnose because of either a positive SARS-CoV-2 RT-PCR (100% of cases) or a

positive chest CT-scan (100% of cases) thus yielding a shorter delay (1 day \pm 3.3) between the onset of neurological symptoms and the biologically confirmed COVID-19 diagnosis.

Cerebrovascular events

Cerebrovascular events were the other challenging neurological presentations of COVID-19: the RT-PCR for SARS-CoV-2 was not systematically positive (66.7%) and the mean delay between stroke onset and the COVID-19 diagnosis was 2.7 days \pm 5.2. Noteworthy, a typical SARS-CoV-2 pneumonia was found in all cerebrovascular event cases.

Other CNS and PNS presentations

Other neurological conditions affecting either the CNS or the PNS appeared easier to attribute to COVID-19, provided the clinician had prescribed SARS-CoV-2 specific tests (RT-PCR and/or serology) in the context of the pandemic. In these neurological presentations, the diagnostic of COVID-19 was often available before the onset of the neurological symptom.

Using chest CT-scan as a diagnostic criterion of COVID-19

Using the presence of typical signs of SARS-CoV-2 pneumonia on chest CT-scan as an additional criterion in favor of COVID-19 during the first wave of the pandemic shortened the delay between the onset of neurological symptoms and the diagnostic confirmation of the infection (one-sided paired t-test, $p = 0.013$). Overall, this delay was 0.8 days \pm 5.6 for the whole sample, 2.1 days \pm 5.7 for the encephalitis group, 0.8 days \pm 3.3 for the encephalopathy group, 1.8 days \pm 5.1 for cerebrovascular events and did not change for the two other CNS and PNS groups.

Discussion

This monocentric retrospective case series showed the broad clinical spectrum of neurological disorders associated with SARS-CoV-2 infection. We identified different neurological manifestations ranging from mild to more severe, affecting either CNS or PNS, and requiring either limited care or a

prolonged stay in hospital. Three patients (mean age 79.7 years) in this series died, due to complications of SARS-CoV-2 pneumonia.

The neurological presentations of COVID19 usually occurred several days or weeks after the SARS-CoV-2 infection onset. CNS infestation was not proven in these neurological cases. CSF testing for RT-PCR for SARS-CoV-2 was negative in the 17 patients for which this assay was performed. Such negative results are in line with previously reported studies,(1) with very few exceptions.(3,23,24) Here, we stress the importance of the inflammatory syndrome observed in encephalitis and encephalopathy cases, along with systemic disorders affecting the kidney, the liver and muscles. This inflammatory syndrome was present at the onset of the infection, but tended to worsen after a few days when the cognitive and behavioral manifestations of the encephalitis/encephalopathy were severe. This secondary worsening of inflammatory response likely constitutes a key pathological aspect of COVID-19 severity.(25) Secondary improvement of systemic inflammation was associated with favorable neurological outcome, with limited neurological sequelae of encephalitis or encephalopathy in survivors of the disease, although further follow-up cognitive assessment is needed for these patients. Cerebrovascular events associated with COVID-19 occurred in patients with few cardiovascular risk factors, but these patients commonly showed a moderate inflammatory syndrome and some of them had biological stigmata of antiphospholipid syndrome, as already reported in the context of SARS-CoV-2 infection.(26) Other neurological manifestations such as GBS could be related to dysimmune response induced by the SARS-CoV-2 infection.(6) Finally, we are aware that some of the reported CNS manifestations could just have coincidentally occurred during simultaneous COVID-19 without any causal link between the two affections. Larger epidemiological studies might better test for this hypothesis.

The diagnosis of COVID-19 infection was often delayed in case of encephalitis and cerebrovascular event because RT-PCR for SARS-CoV-2 in nasopharyngeal swabs were not positive in all cases at the time of neurological examination. This delayed diagnosis has practical consequences for the clinician, as it increases the risk of transmitting SARS-COV-2 to other patients and to health care professionals. In the context of the COVID-19 pandemic, supplementary caution should be paid *a priori* with

systematic use of masks and other barrier gestures to minimize the risk. Single rooms should be preferred for new patients with neurological symptoms. Chest CT-scans have been useful in this series, to demonstrate typical SARS-CoV-2 pneumonia, even in the absence of severe respiratory dysfunction. The discovery of typical signs of SARS-CoV-2 pneumonia has been used as a surrogate diagnostic criterion for COVID-19 during the first wave of the pandemic and may help shorten the delay between the neurological disorder onset and the diagnosis of SARS-CoV-2 infection. Finally, specific IgG antibodies against SARS-CoV-2 were positive in all patients with available sera. As these tests are now widely available, their use in clinical practice should be generalized to better ascertain *a posteriori* the diagnosis in disputable cases.

Conclusion

The diagnosis of neurological disorders associated with SARS-CoV-2 infection is a challenge for neurologists. Based on the experience that RT-PCR assay for SARS-CoV-2 infection in nasopharyngeal swabs is not systematically positive at the time of the neurological symptom, we encourage clinicians to repeat RT-PCR assay when an initial search has been negative and to associate a chest CT-scan and SARS-CoV-2 antibodies to track for COVID-19 diagnosis in patients with suspected neurological manifestations of COVID-19. Before reaching the diagnosis of neurological presentations of COVID-19, clinicians might apply *a priori* protection measures for any new patient to limit the nosocomial threat for the hospital community.

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Table 1. Demography and profiles of patients with neurological manifestations of COVID-19

	All patients	Encephalitis	Encephalopathy	Cerebrovascular event	Other CNS	PNS
Number of cases	26	8	6	6	4	2
Demographics						
Age, mean ± SD (min, max)	58.3 ± 19.3 (16-86)	57.8 ± 11.3 (36-69)	74.8 ± 11.9 (55-86)	57.3 ± 20.9 (34-82)	39.8 ± 23.6 (16-69)	50.5 ± 26.2 (32-69)
Sex (M/F)	19/7	7/1	6/0	4/2	2/2	0/2
Comorbidities: N (%)						
Hypertension	10 (38.5)	5 (62.5)	3 (50)	0 (0)	1 (25)	1 (50)

Diabetes	5 (19.2)	2 (25)	2 (33.3)	0 (0)	0 (0)	1 (50)
Renal dysfunction	4 (15.4)	3 (37.5)	1 (16.7)	0 (0)	0 (0)	0 (0)
Cardiac dysfunction	5 (19.2)	3 (37.5)	1 (16.7)	0 (0)	1 (25)	0 (0)
Obesity	3 (11.5)	1 (12.5)	2 (33.3)	0 (0)	0 (0)	0 (0)
Dyslipidemia	7 (26.9)	2 (25)	4 (66.7)	0 (0)	0 (0)	1 (50)
Tobacco use	5 (19.2)	1 (12.5)	1 (16.7)	2 (33.3)	1 (25)	0 (0)
Asthma or COPD	2 (7.7)	0 (0)	1 (16.7)	1 (16.7)	0 (0)	0 (0)
Previous stroke	1 (3.8)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)
Cognitive impairment	3 (11.5)	0 (0)	1 (16.7)	2 (33.3)	0 (0)	0 (0)
Severity outcomes						
ARDS / ICU N (%)	4/ (15.4)	2 (25)	1 (16.7)	1 (16.7)	0 (0)	0 (0)
Fatal outcome, N (%)	3 (11.5)	0 (0)	2 (33.3)	1 (16.7)	0 (0)	0 (0)
Hospital stay, days mean \pm SD	14.3 \pm 11.4	20.8 \pm 14.0	11.2 \pm 6.1	14.3 \pm 11.5	9.0 \pm 9.1	6.0 \pm 8.5
Blood Oxygen saturation % mean \pm SD	92.7 \pm 7.1	91.5 \pm 4.2	90.2 \pm 4.1	91 \pm 12.4	98.0 \pm 1.6	99.0 \pm 0
Biomarkers, mean (SD)						
Leucocytes /mm ³ (4000 < N < 10000)	8086 \pm 3083	10387 \pm 4052	6900 \pm 1671	7742 \pm 1480	7075 \pm 1676	5500 \pm 4525
Lymphocytes /mm ³ (1000 < N < 4000)	1002 \pm 700	925 \pm 420	533 \pm 280	1128 \pm 773.3	1550 \pm 1240	1300 \pm 566
C-Reactive protein mg/L (N < 5)	98.4 \pm 103.9	155.3 \pm 120.6	167.6 \pm 91.5	37.3 \pm 20.2	19.9 \pm 38.7	3.0 \pm 3.5
Fibrinogen mg/L (2 < N < 4)	5.6 \pm 2.5	7.1 \pm 2.5	7.1 \pm 0.8	5.0 \pm 2.5	2.9 \pm 0.5	3.6 \pm 0.8
Ferritin μ g/L (30 < N < 400)	1734 \pm 2079	2456 \pm 2317	2573 \pm 2452	552 \pm 439	95 \pm 75	154
D-Dimers ng/mL (N < 500)	3794 \pm 3210	2618 \pm 1068	4414 \pm 4920	5134 \pm 4277	-	-
Creatinine μ mol/L (N < 106)	221.9 \pm 412.4	489.3 \pm 679.8	156.2 \pm 180.6	80.7 \pm 17.4	72.8 \pm 11.5	71.5 \pm 4.9
AST UI/L (N < 50)	58.5 \pm 63.8	93.6 \pm 89.5	70.2 \pm 59.1	26.0 \pm 11.4	30.8 \pm 22.2	20.0 \pm 1.4
ALT UI/L (N < 50)	47.8 \pm 47.1	63.8 \pm 58.1	67.3 \pm 59.3	23.2 \pm 10.9	27.3 \pm 23.3	28.0 \pm 8.5
Creatine Kinase UI/L (N < 308)	592.6 \pm 1847.6	1389 \pm 3091	159.8 \pm 61.2	130.6 \pm 126.1	410.5 \pm 439.1	41.5 \pm 13.4
CSF Cells /mm ³ (N < 5)	8.9 \pm 20.0	18.8 \pm 32.7	1.3 \pm 1.2	7.3 \pm 4.0	4.3 \pm 3.5	0

CSF Glucose mmol/L (2.2 < N < 3.9)	3.7 ± 1.3	3.2 ± 1.8	4.5 ± 0.9	3.5 ± 0.2	4.1 ± 1.5	4.4 ± 1.4
CSF Proteins g/L (0.15 < N < 0.45)	0.7 ± 0.6	0.6 ± 0.5	0.5 ± 0.2	0.6 ± 0.0	0.5 ± 0.2	1.5 ± 1.7
CSF positive SARS-CoV-2 RT-PCR N/total (%)	0/17 (0)	0/6 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/2 (0)

Abbreviations: acute respiratory distress syndrome (ARDS), intensive care unit (ICU), central nervous system (CNS), peripheral nervous system (PNS), chronic obstructive pulmonary disease (COPD), standard deviation (SD), aspartate aminotransferase (AST), alanine aminotransferase (ALT), cerebrospinal fluid (CSF)

Table 2. Clinical symptoms and tests allowing the diagnosis of neurological presentation of COVID-19

	All patients	Encephalitis	Encephalopathy	Cerebrovascular event	Other CNS	Guillain-Barré syndrome
N	26	8	6	6	4	2
Diagnostic methods, N/Total number of patients probed with the diagnostic test (%)						
Positive nasopharyngeal SARS-CoV-2 RT-PCR	18/25 (72)	4/8 (50)	6/6 (100)	4/6 (66.7)	3/3 (100)	1/2 (50)
Positive SARS-Cov-2 IgG	13/13 (100)*	5/5 (100)	-	4/4 (100)	2/2 (100)	2/2 (100)
SARS-CoV-2 pneumonia on Chest CT-scan	19/22 (86.4)	6/7 (85.7)	6/6 (100)	6/6 (100)	0/1 (0)	1/2 (50)
Symptoms suggestive of COVID-19 infection, N (%)						
COVID-19 contact	9 (34.6)	2 (25)	3 (50)	2 (33.3)	1 (25)	1 (50)
Fever > 38.5°C	16 (61.5)	7 (87.5)	5 (83.3)	3 (50)	0 (0)	1 (50)
Dyspnea	9 (34.6)	2 (25)	4 (66.7)	3 (50)	0 (0)	0 (0)
Hypoxia (<93%)	9 (34.6)	3 (37.5)	4 (66.7)	2 (33.3)	0 (0)	0 (0)
Anosmia/ageusia	10 (38.5)	4 (50)	1 (16.7)	2 (33.3)	2 (50)	1 (50)
Cephalalgia	11 (42.3)	4 (50)	1 (16.7)	2 (33.3)	3 (75)	1 (50)
Asthenia	16 (61.5)	6 (75)	5 (83.3)	2 (33.3)	2 (50)	1 (50)
Anorexia	10 (38.5)	4 (50)	4 (66.7)	1 (16.7)	1 (25)	0 (0)
Diarrhea	9 (34.6)	3 (37.5)	3 (50)	2 (33.3)	0 (0)	1 (50)
Delays, days, mean ± SD (min, max)						
From COVID-19 symptoms onset to neurological syndrome onset	8.2 ± 8.8 (0, 36)	5.9 ± 4.0 (0, 13)	5.7 ± 3.2 (3, 11)	7.2 ± 8.7 (0, 20)	16.0 ± 15.9 (0, 36)	12.0 ± 17.0 (0, 24)
From neurological symptoms onset to hospitalization#	0.0 ± 3.7 (-8, 9)	-0.1 ± 5.7 (-8, 7)	-1.0 ± 2.4 (-4, 1)	-0.3 ± 1.0 (-2, 1)	0.3 ± 0.5 (0,1)	4.5 ± 6.4 (0, 9)

From neurological symptoms onset to proven COVID-19 diagnosis\$	1.6 ± 5.4 (-13, 13)	3.9 ± 4.0 (0, 10)	1.0 ± 3.3 (-4, 6)	2.7 ± 5.2 (-1,13)	-1.5 ± 6.4 (-11, 3)	-3.5 ± 13.4 (-13, 5)
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*Six patients had both a positive RT-PCR and a positive serology for SARS-CoV-2. SD: standard deviation. # negative values suggest that neurological symptoms occurred in patients already admitted in hospital. \$ negative values suggest that proven diagnosis of COVID-19 was available before neurological symptoms onset.