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Retrospective Observational Study of Brain Magnetic Resonance Imaging Findings in Patients with Acute SARS-CoV-2 Infection and Neurological Manifestations

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Key Results

1. Of the 73 patients who presented neurological symptoms, 43 had pathological MRI findings (58.9%), including 17 with acute ischemic infarcts (23.3%), 1 with a deep venous thrombosis (1.4%), 8 with multiple microhemorrhages (11.3%), 22 with perfusion abnormalities (47.7%), 3 with restricted diffusion foci within the corpus callosum consistent with cytotoxic lesions of the corpus callosum (CLOCC, 4.1%).
2. Imaging patterns possibly related to COVID-19 were observed in patients in intensive care and included multifocal white matter enhancing lesions seen (4 patients, 5%) and basal ganglia abnormalities (4 patients, 5%).

Summary Statement

MRI abnormalities included cerebrovascular lesions, perfusion abnormalities, cytotoxic lesions of the corpus callosum, ICU-related complications, white matter enhancing lesions and basal ganglia abnormalities.

Abbreviations

CLOCC: Cytotoxic lesions of the corpus callosum; CNS: central nervous system; COVID-19: coronavirus disease 2019; CT: computed tomography; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; PRES: posterior reversible encephalopathy syndrome; RT-PCR: reverse-transcriptase–polymerase-chain-reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Key words: COVID-19; SARS-CoV-2; neurological manifestations; brain MRI; imaging patterns

Abstract

Background: This study provides a detailed imaging assessment in a large series of COVID-19 patients with neurological manifestations.

Purpose: To review the MRI findings associated with acute neurological manifestations in COVID-19 patients.

Methods: This was a cross-sectional study conducted between March 23 and May 7, 2020 at the Pitié-Salpêtrière University Hospital, a reference center for COVID-19 in the Paris area. Inclusion criteria were: adult patients diagnosed with SARS-CoV-2 infection, presenting with acute neurological manifestations and referred for a brain MRI examination. Patients were excluded if they had a previous history of neurological disease. The characteristics and the frequency of different MRI features were investigated. The findings were analyzed separately in patients in intensive care units (ICU) and other departments (non-ICU).

Results: During the inclusion period, 1176 consecutive patients were hospitalized for suspected COVID-19. Out of 308 patients with acute neurological symptoms, 73 patients met the inclusion criteria (23.7%) and were included: 35 ICU patients (47.9%) and 38 non-ICU patients (52.1%). The mean age was 58.5 ± 15.6 years, with a male predominance (65.8% vs. 34.2%). Forty-three patients presented pathological MRI findings 2-4 weeks after symptom onset (58.9%), including 17 with acute ischemic infarct (23.3%), 1 with a deep venous thrombosis (1.4%), 8 with multiple microhemorrhages (11.3%), 22 with perfusion abnormalities (47.7%), 3 with restricted diffusion foci within the corpus callosum consistent with cytotoxic lesions of the corpus callosum (CLOCC, 4.1%). Multifocal white matter enhancing lesions were seen in 4 ICU patients (5%). Basal ganglia abnormalities were seen in

4 other patients (5%). The cerebrospinal fluid (CSF) analysis was negative for SARS-CoV-2 in all tested patients (n=39).

Conclusion: In addition to cerebrovascular lesions, perfusion abnormalities, CLOCC and ICU-related complications, we identified two patterns including white matter enhancing lesions and basal ganglia abnormalities that could be related to SARS-CoV-2 infection.

Introduction

Since the coronavirus disease 2019 (COVID-19) outbreak in December 2019, there is growing evidence that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has central nervous system (CNS) involvement in addition to the primary respiratory target. In a series of 214 patients infected with SARS-CoV-2, more than a third of patients had neurological manifestations, such as stroke, seizures and anosmia (1). Clinical reports (2–4) and experiments (5,6) from the previous coronavirus epidemics, namely the severe acute respiratory syndrome (SARS-CoV) in 2002 and the Middle East Respiratory Syndrome (MERS-CoV) in 2012, have established that coronaviruses have a neurotropic and neuroinvasive potential. Coronaviruses enter the CNS using a hematogenous pathway or through the olfactory bulb or peripheral nerves (5,6). Using mice models, the infection has been shown to start in the respiratory epithelium, then spread to the brain via the olfactory bulb, and gradually invade the subcortical and cortical regions (5–7). This olfactory involvement could explain the anosmia observed in a large number of COVID-19 patients. Proposed pathophysiological mechanisms include a direct viral replication and an immune-mediated reaction (5,6). It is not yet known whether this knowledge applies to the new SARS-CoV-2. So

far, several imaging findings have been described in the setting of COVID-19, but the relationship with SARS-CoV-2 remains unclear (8–14).

This study reports a series of patients with acute neurological manifestations admitted for COVID-19 and referred for a brain MRI in a Parisian reference center for the disease. We describe the MRI findings and their frequency and investigate whether imaging patterns possibly related to COVID-19 could be identified. These patterns were considered as possibly related to COVID-19 when 1) they were found in ≥ 3 patients, 2) they were similar across patients, and 3) they were not explained by another pathology or condition.

Material and Methods

Study Design and Participants

The study was conducted according to good clinical practice, sponsored by Assistance Publique-Hôpitaux de Paris, and received approval from the local Sorbonne University Hospital Ethics Committee (CER-202028 on 24/04/2020). All patients or their relative signed written informed consent for the use of their medical data in accordance with the French regulation and the European General Data Protection Regulation (GDPR). The study was registered in the clinicaltrial.gov website (NCT04362930). Patients referred for brain MRI in the context of COVID-19 between March 23 and May 7, 2020 were assessed in the Neuroradiology department of the Pitié-Salpêtrière Hospital, a tertiary neurology center and reference center for COVID-19. The inclusion criteria were: i) diagnosis of SARS-CoV-2 infection by detection of RNA in a nasopharyngeal swab, bronchial aspiration or bronchoalveolar lavage using reverse-transcriptase–polymerase-chain-reaction (RT-PCR) or by chest computed tomography (CT) showing results consistent with SARS-CoV-2-associated pneumonia, ii) presence of acute neurological symptoms, iii) age greater than 18 years and

iv) availability of a brain MRI. The exclusion criteria were: i) underlying progressive CNS disease excluding stroke, ii) alternative diagnosis assessed during the MRI examination. A case of deep venous thrombosis from the current series has previously been published (15).

Data Collection

Clinical data collected by expert neurologists, electroencephalogram (EEG), cerebrospinal fluid (CSF) and chest CT findings were retrospectively extracted from electronic medical records. Difficult cases were discussed in multidisciplinary meetings.

MRI Acquisition

Patients were scanned using a 3.0 Tesla MRI system (PREMIER, General Electric Healthcare) with a 48-channel receive head coil. The protocol included three-dimensional (3D) T1-weighted (Magnetization-prepared rapid acquisition with gradient-recalled echo, MPRAGE) and 3D Fluid-attenuated inversion recovery (FLAIR) images, susceptibility-weighted imaging (SWI), 3D pseudo-continuous arterial spin labeling (ASL) perfusion imaging, diffusion-weighted imaging (DWI) sequence, 3D post-gadolinium spin echo T1-weighted imaging. In case of suspicion of acute stroke, axial FLAIR sequence, DWI, SWI, ASL and arterial 3D time-of-flight were acquired.

Image Analysis

Two neuroradiologists (L.C., N.P.) independently analyzed all MRI images. In case of disagreement, images were reviewed and a consensus was reached. The following imaging characteristics were evaluated: diffusion abnormalities, white and gray matter FLAIR signal abnormalities, ASL perfusion abnormalities, parenchymal and meningeal enhancement,

hemorrhages, vessel permeability, cranial nerve abnormalities including thickening, abnormal T2 hyperintensity and contrast enhancement.

Statistical Analysis

The age was expressed as mean and standard deviation. Categorical variables were expressed as counts and percentages. Participants were divided into an “ICU” group, including patients hospitalized or discharged from an ICU, and a “non-ICU” group, with patients never hospitalized in ICU. The age was compared between groups using Student’s t-test. Proportions for categorical variables were compared using Pearson's Chi-squared test or Fisher's Exact Test. Statistical analyses were performed with R software (version 3.6.1). The significance threshold was set at a $p < 0.05$.

Results

Patient Recruitment

During the inclusion period, 1176 consecutive patients were hospitalized for suspected COVID-19 in the Pitié-Salpêtrière Hospital. Three hundred and eight of these patients (26.2%) presented with neurological and/or psychiatric manifestations, out of whom 223 had *de novo* acute neurological symptoms (i.e. no previous history of neurological disease) (72.4%). Seventy-three patients met the inclusion criteria (73/223, 32.7%). In these 73 patients, RT-PCR was positive in 67 patients (91.8%). In the 6 remaining patients with negative SARS-CoV-2 RT-PCR (8.2%), chest CT scans were highly suggestive of SARS-CoV-2-associated pneumonia. Thirty-five patients were ICU patients (47.9%) and 38 were non-ICU patients (52.1%). Patient flow chart is detailed in Figure 1.

Patient Characteristics

Patient characteristics are summarized in Table 1. The mean age was 58.5 ± 15.6 years (65.8% male), without difference between non-ICU and ICU patients. MRI examinations were performed 22.3 ± 15.7 days (range: 0-65 days, significantly longer in the ICU group, $p < 0.001$) after the onset of COVID-19 symptoms and 5.9 ± 6.7 days (range: 0-30) after from the onset of neurological symptoms. The most frequent neurological manifestations were impaired consciousness not explained by therapy (39/73, 53.4%), focal neurological deficit (31/73, 42.5%) and seizure (10/73, 13.7%). ICU patients had significantly more impaired consciousness than non-ICU patients (85.7% vs. 23.7%, $p < 0.001$), but no difference in the rate of seizures and focal deficits. CSF analysis was available for 39 patients (39/73, 53.4%) showing mild pleiocytosis (8/37, 21.6%) hyperproteinorachia (10/35, 28.6%), oligoclonal bands (2/12, 16.7%) or mild Interleukin 6 increase (8/11, 72.7%). For all patients, RT-PCR for the SARS-CoV-2, herpes simplex viruses 1 and 2, varicella-zoster virus, cytomegalovirus and Epstein-Barr virus as well as the bacterial culture were negative in the CSF. EEG analysis was available for 40 patients (40/73, 54.8%), showing pathological findings related to seizure or encephalopathy in 9 patients (9/40, 22.5%; 2 non-ICU and 7 ICU) and non-specific findings in 24 patients (24/40, 60.0%. 9 non-ICU and 15 ICU). Clinical characteristics of the other non-included patients are provided in Table E1.

MRI Findings

MRI exams revealed no significant abnormalities in 30 patients (22 non-ICU and 8 ICU), apart from changes usually seen in elderly patients, and pathological findings in 43 patients (43/73, 58.9%). Seventeen patients presented with acute ischemic infarct, 1 with a deep venous thrombosis, 8 with multiple microhemorrhages, 9 with seizure-related perfusion abnormalities, 10 with isolated perfusion abnormalities, 4 with multifocal enhancing white

matter lesions, 3 with restricted diffusion foci within the splenium of the corpus callosum, 3 with hypoxic-ischemic lesions, 2 with posterior reversible encephalopathy syndrome (PRES), 3 with metabolic abnormalities and 2 with neuritis (Table 2). Clinical details for patients with white matter lesions and basal ganglia abnormalities are presented in Table E2.

Cerebrovascular complications

Stroke

Twelve of the 17 patients with acute ischemic infarct (70.6%) had multiple ischemic foci while 8 (47.0%) had a territorial infarction (Supplementary Figure E1). Three patients had both types of lesions. There was no significant difference between non-ICU and ICU patients ($p=0.638$).

Deep cerebral vein thrombosis

Extensive deep cerebral venous thrombosis complicated by hemorrhagic venous infarction was diagnosed in a 72-year-old male ICU patient without known risk factor for thrombosis and with normal baseline coagulation tests (Table E3).

Microhemorrhages

ICU patients had a greater number of multiple microhemorrhages (≥ 5) than non-ICU patients (20.6% vs. 2.7%, $p=0.017$), involving the corpus callosum in 5 patients (Figure 2). Patients with microhemorrhages tended to have increased partial thromboplastin time due to preventive anticoagulation therapy (Table E3). Anticoagulation overdose occurred in one ICU patient. Two ICU patients with multiple microhemorrhages (28.6%) had an extracorporeal membrane oxygenation (ECMO).

Perfusion abnormalities

Twenty-two out of 46 patients (47.8%) presented perfusion abnormalities that were related to seizure in nine patients (19.6%), recent or old vascular lesions in four patients (8.7%) and

that were unrelated to seizures or ischemia in 10 patients (21.7%). In two patients, perfusion abnormalities were attributed to both seizures and ischemia. ICU patients had more perfusion abnormalities than non-ICU ones (62.5% vs. 31.8%, $p=0.037$), with a higher rate of isolated perfusion abnormalities (33.3% vs. 9.1%, $p=0.046$). In particular, marked post-ictal changes associating edema and diffusion restriction within the right frontobasal cortex were observed in a 69-year-old ICU patient who presented with status epilepticus (Supplementary Figure E2).

White matter enhancing lesions

Four ICU patients with late awakening after sedation withdrawal had multifocal bilateral deep and periventricular white matter lesions associated with an enhancement along the perivascular spaces. These lesions had a vacuolated necrotic appearance in one patient (Figures 3 and 4).

Basal ganglia abnormalities

Basal ganglia abnormalities were seen in four other ICU patients who also had late awakening after sedation withdrawal, including diffusion restriction with FLAIR hyperintensity of the substantia nigra, bilateral enhancement with moderate diffusion restriction in the globus pallidus, and bilateral spontaneous hyperintensity on T1-weighted images in the globus pallidus in one patient and in the upper part of the striatonigral pathways in another patient (Figure 5).

Corpus callosum abnormalities

Restricted diffusion foci within the splenium of the corpus callosum were evidenced in three patients. Enhancement was seen in one patient (in the two other patients referred for suspected ischemia, contrast administration was not performed). In one case, diffusion imaging normalized in the follow-up MRI 25 days later. Follow-up MRI was not performed in

the other two patients. This aspect suggested Cytotoxic Lesions of the Corpus Callosum (CLOCC, Supplementary Figure E3).

PRES

Typical findings of PRES with parieto-occipital and superior frontal swelling reversible on the follow-up MRI were detected in one ICU patient. Reversible swelling involving the midbrain and basal ganglia also consistent with PRES was seen in another ICU patient with multiple organ failure (Figure 6).

Hypoxic-ischemic lesions

Hypoxic-ischemic lesions were seen in three ICU patients with a history of cardiopulmonary arrest (one case) or severe low flow (two cases).

Metabolic changes

Pontine white matter abnormalities consistent with osmotic demyelination syndrome (central pontine myelinolysis) were detected in three ICU patients with a history of hydrolytic disturbances.

Meningeal enhancement

Meningeal enhancement was detected in only two ICU patients, including dural involvement in two patients who previously had a lumbar puncture, and leptomeningeal involvement in one patient.

Discussion

Neuroimaging examinations at 2-4 weeks after symptom onset in 73 COVID-19 patients with acute *de novo* neurological manifestations showed ischemic lesions, diffuse microhemorrhages involving the corpus callosum, deep vein thrombosis, perfusion abnormalities, CLOCC and other ICU-related complications, and two other patterns including contrast-enhanced white matter lesions and abnormalities involving the basal ganglia. .

The pattern of **white matter enhancing lesions** observed in four patients differed from the one seen in acute disseminated encephalomyelitis (ADEM) where lesions tend to be asymmetrical, with variable involvement of gray matter and punctate or ring enhancement (16–18). Several features also argued against the diagnosis of subacute embolic infarctions, including i) the periventricular topography of lesions, ii) their morphology associating an oval shape and ill-defined margins, and iii) the perivascular distribution of enhancement. This latter feature has been described in vasculopathies such as PRES and Susac syndrome, and in disorders with angiocentric infiltrates, especially in neurolyupus and neurosarcoidosis (19) and in CD8 encephalitis in HIV patients (20). Similarly, our pattern of white matter enhancing lesions could somehow reflect a vasculitis-like phenomenon and/or an inflammatory disorder with angiocentric involvement (19,20). This pattern has also been observed in a recent study (9), reinforcing the hypothesis of a COVID-19-related damage.

Basal ganglia involvement seen in four patients included signal and diffusion abnormalities, with variable contrast enhancement, affecting the substantia nigra, the globus pallidus and the striatonigral pathway in a variable manner. To our knowledge, this pattern has not been previously reported. Patients with hyperglycemia can present spontaneous T1 hyperintensity within the putamen with variable involvement of the caudate and globus pallidus that is usually unilateral (21). Although patients with T1 hyperintensities in our series were diabetic, the topography that we observed was different (symmetrical and involving the globus pallidus and the upper part of the striatonigral pathways). This pattern of brain damage has some similarities to that seen in encephalitis lethargica (EL) also known as *Von Economo* disease. An epidemic of EL occurred during the 1918 influenza pandemic. In the acute phase, patients with EL had pharyngitis, sleepiness, ocular motility and movement disorders with a fatal presentation in about one third of patients. Delayed parkinsonism and neuropsychiatric

signs may occur (22). Neuropathological studies have shown encephalitis of the midbrain and basal ganglia with lymphocytes infiltration (22–24). MRI examinations revealed bilateral edematous changes within the thalami, basal ganglia and midbrain with variable contrast enhancement (22,23). The substantia nigra was involved in 12% of autopsy cases (22) and in one MRI case (25). Although the etiology of EL is still unknown, infectious and environmental causes have been proposed (24). More recently, examination of archived brain material failed to demonstrate Influenza RNA, while the presence of oligoclonal bands in the CSF and the efficacy of corticosteroids suggested that EL might be immune-mediated (23). Follow-up of the patients with basal ganglia abnormalities in our series will help show whether they develop parkinsonism as seen in the chronic phase of EL (24).

The underlying pathophysiology of these two patterns and their association with COVID-19 remain unclear since SARS-CoV-2 RT-PCR in the CSF was negative in all tested patients. A relationship with COVID-19 appears however possible since these lesions were similarly observed in several patients and were not explained by another pathology or condition. To date, SARS-CoV-2 RNA has been reported positive in the CSF in only three previous patients (9,26,27). Several hypotheses could be formulated to explain PCR negativity in the CSF. First, meningeal contrast enhancement was rare in our series, unlike observations from previous studies (8). This difference could be due to the fact that we acquired the FLAIR images before the administration of contrast (the meningeal contrast enhancement in other cases being reported mainly on post-contrast FLAIR images), or to the lack of meningeal involvement in our series, considering that SARS-CoV-2 could have an intra-neuronal localization as reported with SARS-CoV (28). Second, indirect viral pathogenesis through an immune-mediated mechanism and/or a systemic inflammatory response syndrome could be involved. Such an immune process could also explain the occurrence of neuritis or Guillain-

Barré syndrome (29). Third, the delay between the RT-PCR and the stage of infection could also explain a negative detection. Brain damage may also result from a first step of CNS viral replication, followed by an immune-mediated phenomenon (5,7) where the virus is no longer detectable, as supported by the relatively long delay between the first respiratory symptoms and the neurological impairment in our study. Post-mortem neuropathological examinations in 18 COVID-19 patients only showed hypoxic changes without sign of encephalitis (30). Viral RNA was detected at low levels, possibly due to *in situ* viral RNA from the bloodstream (30). Another neuropathological report evidenced vascular and demyelinating changes in one patient, without mention of virus screening (31). The knowledge collected at this stage would favor the hypothesis of a delayed immune-mediated process underlying the physiopathology of CNS damage (14).

Multiple microhemorrhages have been observed in eight patients, with a specific involvement of the corpus callosum, as recently reported (9,11,32). Hemorrhages are known to be a complication of ECMO (33). Microhemorrhages might have been explained by the presence of ECMO in 2 patients and anticoagulation overdose in another patient. In the remaining patients, the physiopathology could involve microvascular damage. A possible implication of SARS-CoV-2 remains unclear.

Ischemic infarcts were diagnosed in 23.3% of patients of our series. It is now recognized that seriously ill COVID-19 patients are at higher risk of venous and arterial thromboembolic events (34–36) despite prophylactic or curative anticoagulation, compared to non-COVID-19 matched patients (35). The higher percentage in our series compared to previous series (14,37) could be explained by the fact that acute ischemic lesions could have been underestimated on CT scans in previous studies while our study only relied on MRI examinations. Coronaviruses use the angiotensin-converting enzyme 2 (ACE2) to enter cells,

a receptor which is expressed in the epithelia of the lung and small intestine, and also found in brain endothelial cells (5,6). It has been suggested that recruitment of immune cells by direct viral infection of the endothelium or immune-mediated, with a massive inflammatory cascade, may lead to endothelial damage, resulting in stroke, thrombosis and hemorrhage (38).

Perfusion abnormalities, which were related to seizure in 19.6% of patients in our series, were also described in a smaller series (8), although the mechanism was not discussed.

Many factors can account for the occurrence of seizures in COVID-19 patients: fever that lowers the seizure threshold, metabolic alterations, iatrogeny and potential changes related to encephalitis.

Lastly, extensive supratentorial white matter FLAIR hyperintensities (9,11,12) and unilateral abnormalities of the medial temporal lobe (9,26) described in previous studies were not seen in our series.

Our study has several limitations. First, clinical examination was limited in this context and CSF data were only available in about half of the participants. Second, most patients had no prior MRI scan. Finally, at this point, information on the outcome of patients was lacking. A cross-analysis correlating clinical, imaging, CSF and pathological data with patient outcome will be the scope of future studies.

Conclusion

This study provides a detailed description of neuroimaging findings in a series of COVID-19 patients. In addition to cerebrovascular thrombotic events, perfusion abnormalities, CLOCC, microhemorrhages involving the splenium of corpus callosum and ICU-related disorders, two MRI patterns were identified including white matter lesions with perivascular enhancement, that may reflect vasculitis lesions and/or inflammatory lesions with angiocentric

involvement, and basal ganglia abnormalities including substantia nigra involvement. Future imaging-pathological correlation studies will help determine whether there is a causal relationship between COVID-19 and brain MRI lesions. A longitudinal monitoring will also be necessary to assess the long-term neurological impact of COVID-19.

In Press

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Prepress

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Table 1

Patient Characteristics

	Patients with brain MRI (n=73)	Non-ICU (n=38)	ICU (n=35)	p value
Age (y-o), mean ± SD (range)	58.5±15.6 (28-96)	58.1±18.6 (28-96)	58.9±11.7 (35-78)	0.835
Gender, n (%)	48M/25F (65.8/34.2)	22M/16F (57.9/42)	26M/9F (74.3/25.7)	0.140
Delay of MRI examination from the onset of COVID-19 symptoms (days), mean ± SD (range)	22.3±15.7 (0-65)	16.1±12.0 (0-50)	28.5±16.9 (0-65)	<0.001*
Neurological findings, n (%)	/73	/38	/35	
CNS manifestations	69 (94.5)	34 (89.4)	35 (100)	0.048*
Altered consciousness	39 (53.4)	9 (23.7)	30 (85.7)	<0.001*
Confusion	10 (13.7)	9 (23.7)	0 (0)	0.002
Severely impaired consciousness	17 (23.3)	0 (0)	17 (48.6)	<0.001
Coma	3 (4.1)	0 (0)	6 (17.1)	0.007
Delayed awakening after sedation withdrawal	7 (9.6)	0 (0)	7 (20)	0.004
Focal neurological deficit	31 (42.5)	17 (36.8)	14 (40.0)	0.683
Seizure	10 (13.7)	6 (15.8)	4 (11.4)	0.588
Behavioral abnormalities	4 (5.5)	4 (10.5)	—	—
Headache	5 (6.8)	5 (13.2)	—	—
PNS manifestations ¹	7 (9.6)	7 (18.4)	—	—
Peripheral vestibular syndrome	1 (1.4)	1 (2.6)	—	—
Anosmia	4 (5.5)	4 (10.5)	—	—
Decreased visual acuity	1 (1.4)	1 (2.6)	—	—
Guillain-Barre syndrome	1 (1.4)	1 (2.6)	—	—
CSF findings, n/N ² (%)	39/73	19/38	20/35	
High white blood cell (<5 /mm ³)	8/37 (21.6)	3/17 (17.6)	5/20 (25.0)	0.71
Hyperproteinorachia (<0.40 g/L)	10/35 (28.6)	3/16 (18.8)	7/19 (36.8)	0.48
Presence of oligoclonal bands	2/12 (16.7)	2/8 (25.0)	0/4 (0)	1
Intrathecal Immunoglobulin G synthesis	0/7 (0)	0/3 (0)	0/4 (0)	1
Elevated Interleukin-6	8/11 (72.7)	4/4 (100)	4/7 (57.1)	0.66
Elevated Interleukin-10	0/11 (0)	0/4 (0)	0/7 (0)	1

*: $p < 0.05$

¹ PNS examination was limited in ICU patients due to severely impaired consciousness.

² n is the number of patients with positive findings and N the number of patients with available data.

Abbreviations: ICU: intensive care unit; M: male; F: female; SD: standard deviation; CNS: central nervous system; PNS: peripheral nervous system; y-o: year-old;

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Table 2

Patient MRI Findings				
MRI findings, n (%)	Total (n=73)	Non-ICU (n=38)	ICU (n=35)	p value
Ischemic lesions ¹	17/73 (23.3)	8/38 (21.1)	9/35 (25.7)	0.638
Territorial arterial infarct	8 (11.0)	4 (10.5)	4 (11.4)	0.902
Ischemic spots	12 (16.4)	4 (10.5)	8 (22.9)	0.156
Cerebral venous thrombosis	1/73 (1.4)	0/38 (0)	1/35 (2.9)	0.294
Microhemorrhages ²	20/71 (28.2)	7/37 (18.9)	13/34 (38.2)	0.071
0	50 (70.4)	29 (78.4)	21 (61.8)	0.126
≥5	8 (11.3)	1 (2.7)	7 (20.6)	0.017*
Involvement of the corpus callosum	5/71 (7.0)	0 (0)	5 (14.7)	0.016*
Patients with ≥5 on ECMO	2/8 (25.0)	—	2 (28.6)	—
Perfusion abnormalities ³	22/46 (47.8)	7/22 (31.8)	15/24 (62.5)	0.037*
Seizure-related	9 (19.6)	4 (18.2)	5 (20.8)	0.821
Secondary to ischemic lesions	4 (8.7)	1 (4.5)	3 (12.5)	0.339
Isolated	10 (21.7)	2 (9.1)	8 (33.3)	0.046*
Multifocal white matter lesions	4/73 (5.5)	0/38 (0)	4/35 (16.7)	0.032*
Basal ganglia lesions	4/73 (5.5)	0/38 (0)	4/35 (16.7)	0.032*
Substantia nigra	1 (1.4)	0 (0)	1 (2.9)	0.294
Globus pallidus	2 (4.8)	0 (0)	2 (9.5)	0.147
Striatonigral pathway	1 (1.4)	0 (0)	1 (2.9)	0.294
CLOCC ⁴	3/73 (4.1)	1/38 (2.6)	2/35 (5.7)	0.507
PRES	2/73 (2.7)	0/38 (0)	2/35 (5.7)	0.135
Hypoxic-ischemic lesions	3/73 (4.1)	0/38 (0)	3/35 (8.6)	0.065
Central pontine myelinolysis	3/73 (4.1)	0/38 (0)	3/35 (8.6)	0.135
Meningeal enhancement ⁵	2/42 (4.8)	0/21 (0)	2/21 (9.5)	0.147
Corticospinal tracts FLAIR hyperintensity	1/73 (1.4)	0/38 (0)	1/35 (2.9)	0.135
Neuritis ⁶	2/73 (2.7)	2/38 (5.3)	0/35 (0)	0.169

*: p<0.05

¹ Three ICU patients had both territorial ischemic lesions and ischemic spots, associated with cortical necrosis in one patient. No arterial stenosis or thrombosis was associated with territorial strokes.

² No susceptibility- or T2 star-weighted sequence was available in one non-ICU patient and one ICU patient.

The characteristics of the microhemorrhages were consistent with cerebral amyloid angiopathy in one non-ICU patient.

³ ASL was available and interpretable in 46 participants including 22 non-ICU and 24 ICU patients. In two patients, perfusion abnormalities could be attributed both to seizure and ischemia.

⁴ Enhancement of the corpus callosum signal abnormality spot was seen in one patient; no contrast administration was performed in the two other cases

They were potentially related to leukostasis in an ICU patient with chronic lymphocytic leukemia

⁵ Contrast material administration was performed in 42 patients (21 non-ICU and 21 ICU patients). Dural enhancement in two patients was likely due to lumbar puncture; an additional leptomeningeal enhancement was seen with one of these patients.

⁶ Including optic neuritis and vestibulocochlear neuritis.

Abbreviations: ICU: intensive care unit; PRES: posterior reversible encephalopathy syndrome; ECMO: extracorporeal membrane oxygenation; CLOCC: Cytotoxic lesions of the corpus callosum; RT-PCR: reverse-transcriptase–polymerase-chain-reaction; CT: computed tomodensitometry; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Figures

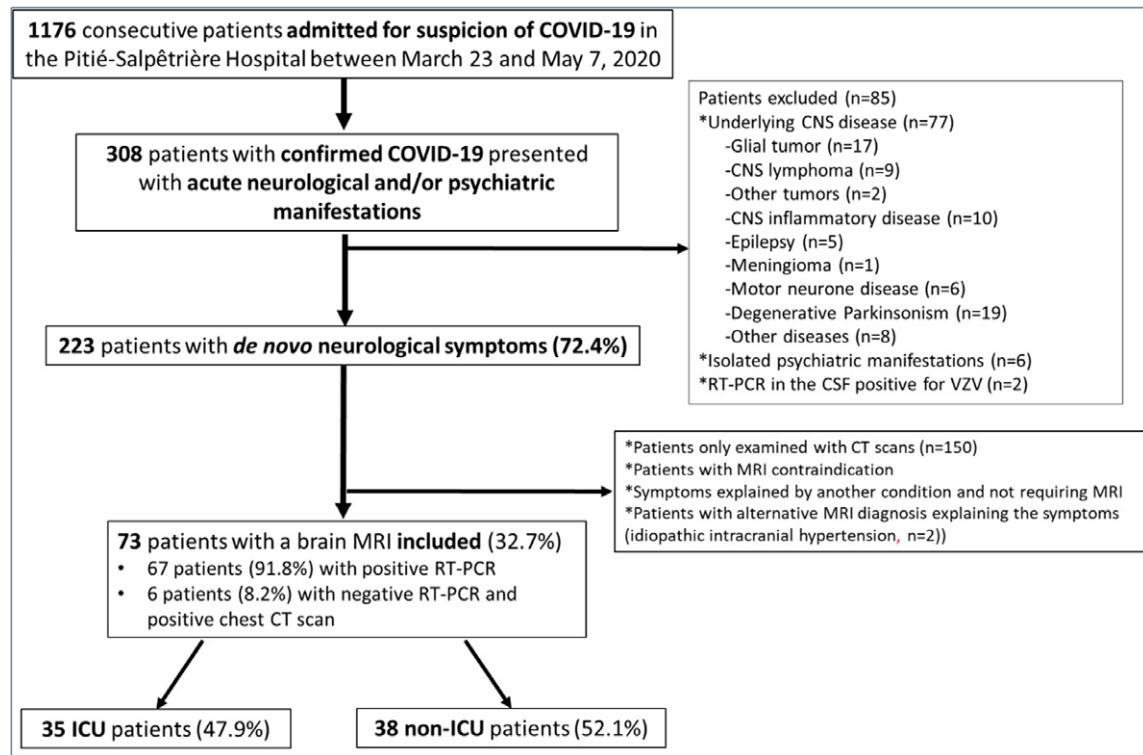


Figure 1: Flowchart of patient inclusion. Abbreviations: CNS: central nervous system; COVID-19: coronavirus disease 2019; CSF: cerebrospinal fluid; CT: computed tomography; ICU: intensive care unit; RT-PCR: reverse-transcriptase–polymerase-chain-reaction.

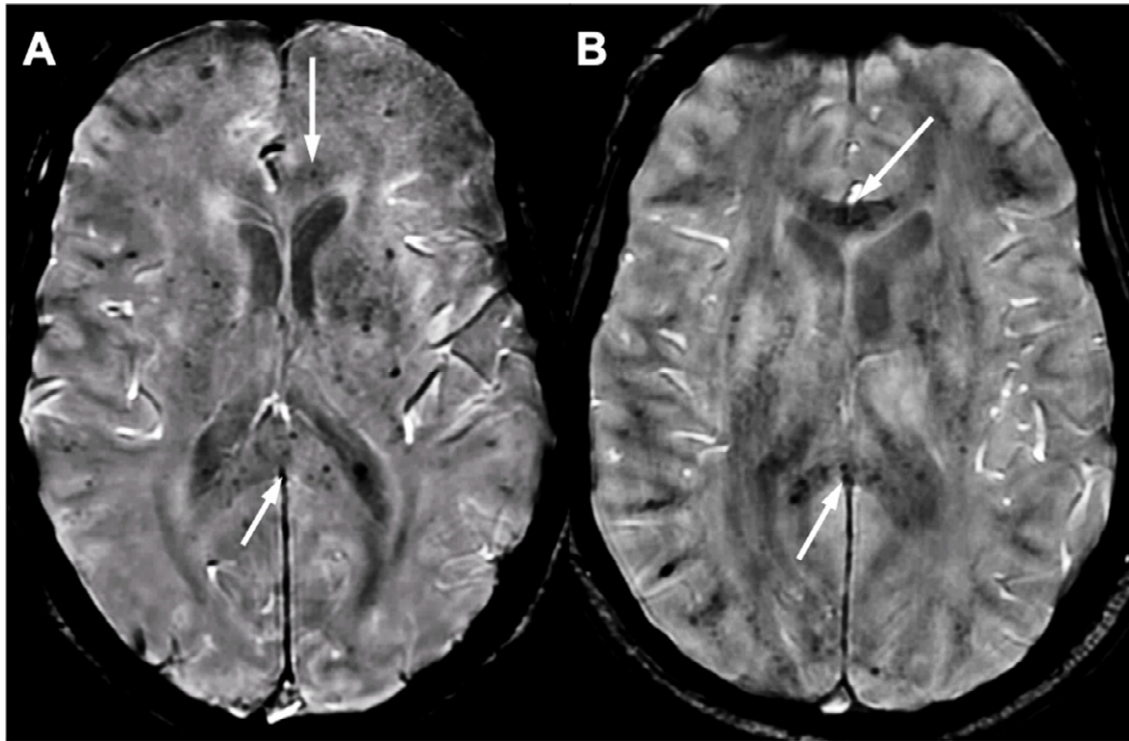


Figure 2: Microhemorrhages. Diffuse microhemorrhages involving the corpus callosum in two patients in intensive care on extracorporeal membrane oxygenation (EMCO, A, arrows) and without ECMO (B, arrows) Abbreviations: ECMO: extracorporeal membrane oxygenation.

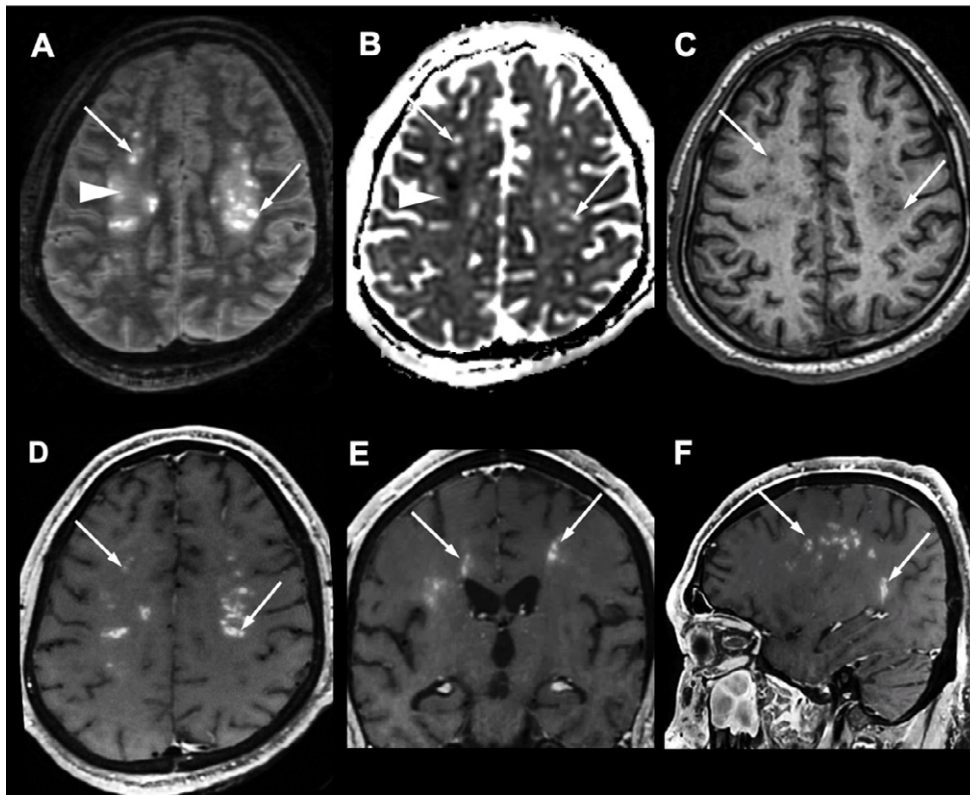


Figure 3: White matter enhancing lesions. A 37-year-old obese male with no medical history, admitted to ICU for SARS-CoV-2-associated pneumonia ten days after the onset of flu-like symptoms, who developed severe acute respiratory syndrome, recurrent venous thromboembolism with negative thrombophilia tests, and multiple organ failure. MRI is performed for late awakening following withdrawal of sedation after 38 days of intensive care. The patient did not recover consciousness and died 42 days after the brain MRI. There were symmetrical multifocal periventricular and deep white matter lesions, hyperintense on axial FLAIR images with a vacuolated appearance (A, arrows), without diffusion restriction (B, arrows), hypointense on T1-weighted images (C, arrows), and with a perivascular enhancement on post-contrast T1-weighted images (D E, F, arrows). These lesions were associated with white matter FLAIR hyperintensities (A, arrowhead) with decreased apparent coefficient diffusion (B, arrowhead). Abbreviations: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

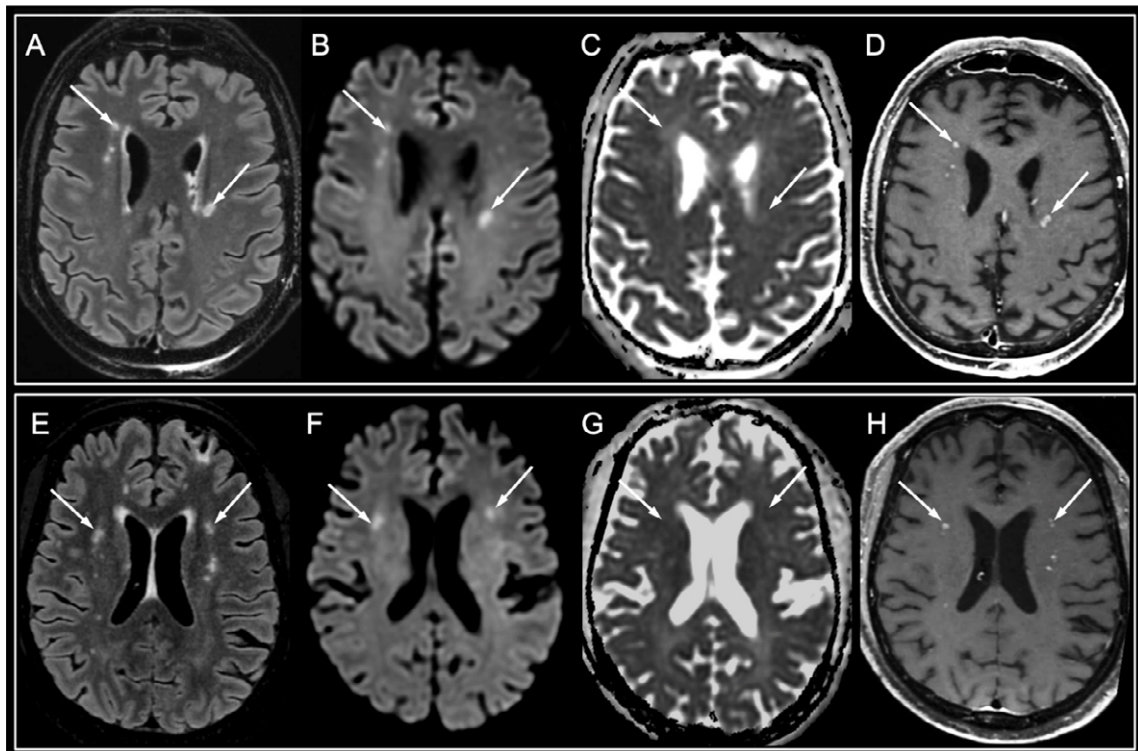


Figure 4: White matter enhancing lesions. A 50-year-old man with a history of kidney transplantation (A-D) and a 50-year-old ICU man with type 2 diabetes (E-H), who presented with late awakening following sedation withdrawal after 39 and 65 days of intensive care for severe hypoxic SARS-CoV-2-associated pneumonia complicated with severe acute respiratory syndrome, respectively. Both patients progressively recovered consciousness and were able to respond to orders. A similar imaging pattern than that in Figure 4 was seen, but with fewer white matter lesions appearing hyperintense on FLAIR images (A, E, arrows) and diffusion-weighted images (B, F, arrows), without apparent diffusion coefficient decrease (C, G, arrows), with a perivascular enhancement on post-contrast T1-weighted images (D, H, arrows). Abbreviation: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

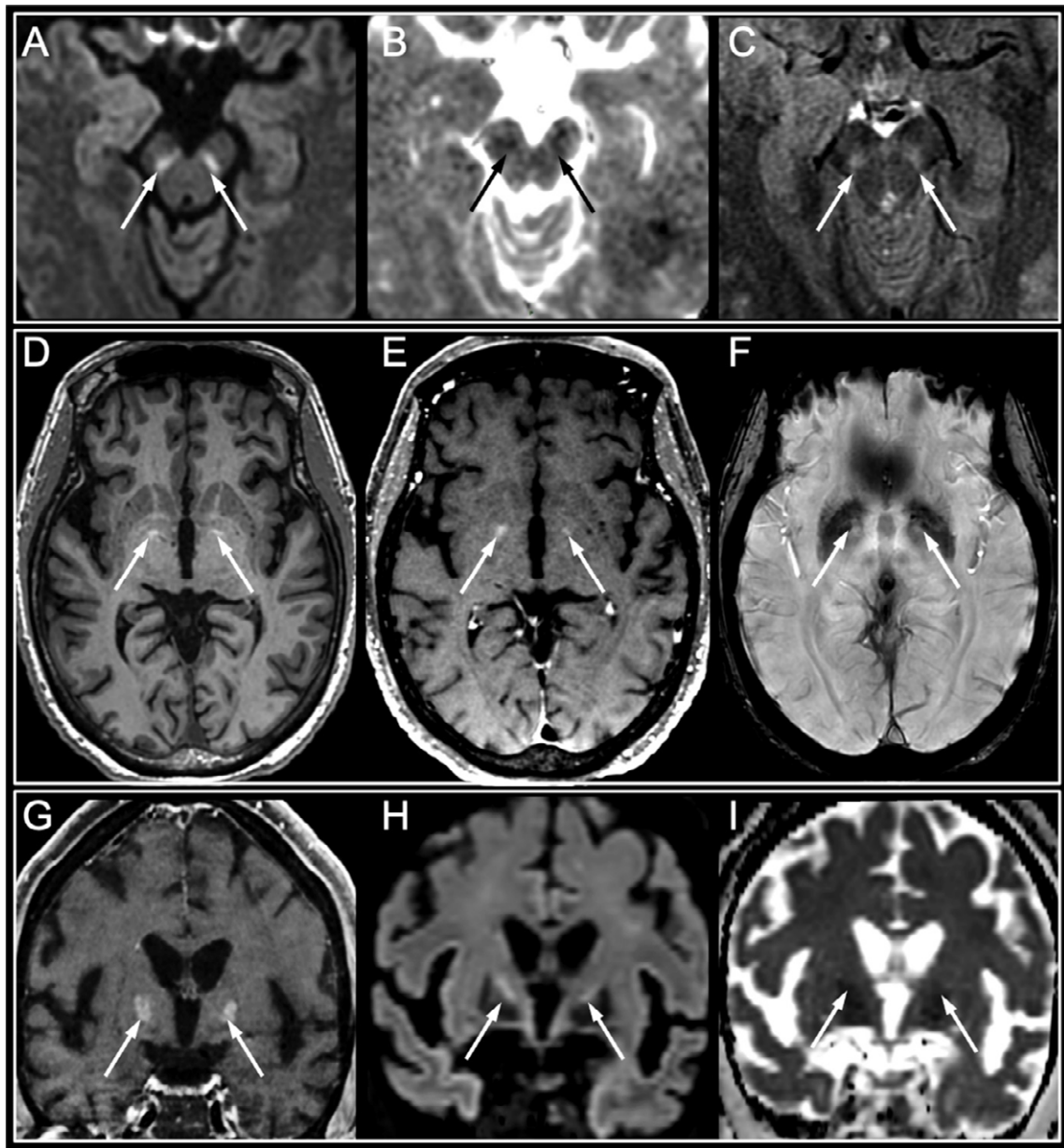


Figure 5: Basal ganglia abnormalities. Basal ganglia abnormalities in three patients who experienced late awakening after sedation withdrawal in a context of SARS-CoV-2 hypoxic pneumonia with severe acute respiratory syndrome:

- 1) A 42-year-old male with untreated chronic lymphocytic leukemia who had tetraparesis upon awakening after 47 days of intensive care (A-C). Hyperintensity on DWI within the substantia nigra (A, arrows) with decreased apparent diffusion coefficient (B, arrows) and hyperintensity on axial FLAIR images (C, arrows) were seen. The follow-up neurological examination showed

complete consciousness recovery with persistent peripheral motor deficit consistent and mild parkinsonian symptoms.

- 2) A 62-year-old diabetic female with chronic cardiovascular disease, who suffered cardiorespiratory arrest after 54 days of intensive care (D-F). Hyperintensity on pre-contrast MP-RAGE axial T1-weighted images in the globus pallidus (D, arrows), with no enhancement on post-contrast T1-weighted images (E, arrows) or hypointensity on susceptibility-weighted images (F, arrows). The follow-up neurological examination also showed complete consciousness recovery with a persistent motor deficit.
- 3) A 56-year-old diabetic and obese female who experienced late awakening after 48 days of intensive care (G-I). Bilateral enhancement within the globus pallidus on coronal post-contrast T1-weighted images (G, arrows), with hyperintensity on diffusion-weighted images (G, arrows) and decreased apparent diffusion coefficient (H, arrows). No follow-up was available.

Abbreviation: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

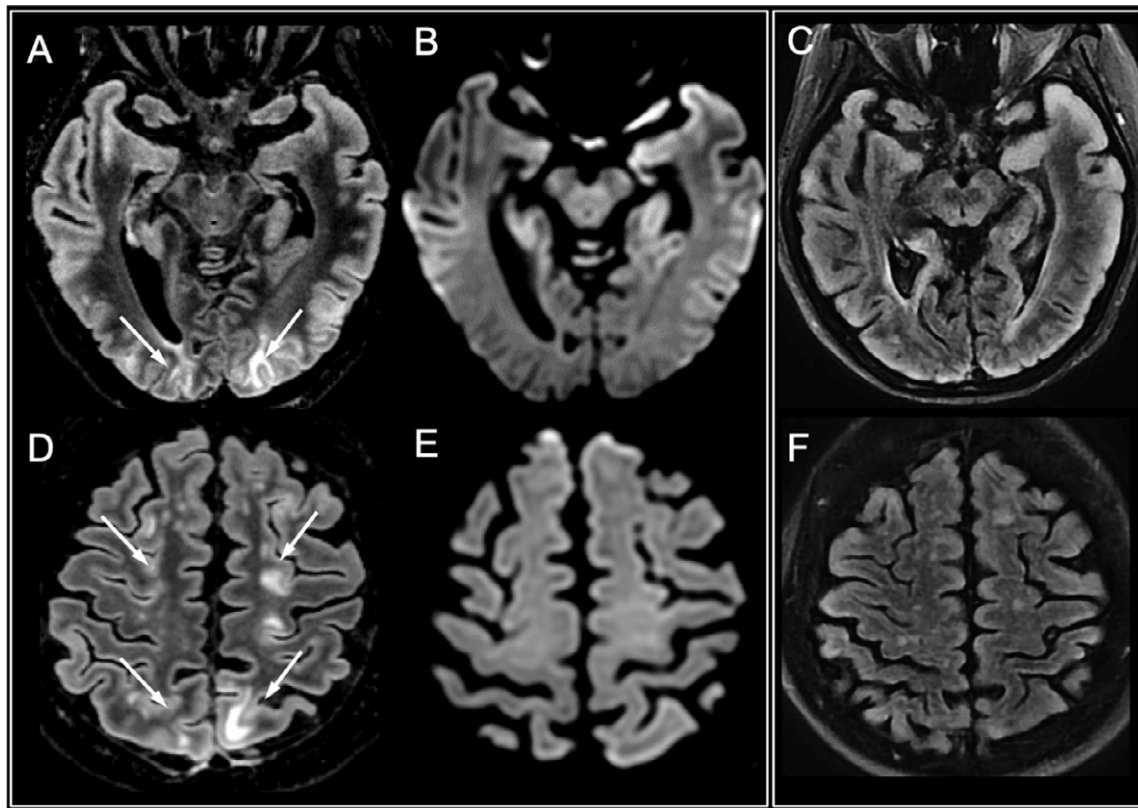


Figure 6: Posterior reversible encephalopathy syndrome (PRES). A 66-year-old male infected with SARS-CoV-2 presenting with status epilepticus in a context of pneumonia and severe hyponatremia. There were cortico-subcortical signal abnormalities in the parieto-occipital and superior frontal regions on FLAIR images (A and D, arrows), with no diffusion restriction (B and E). Follow-up MRI performed ten days later showed complete disappearance of the lesions (C, F).

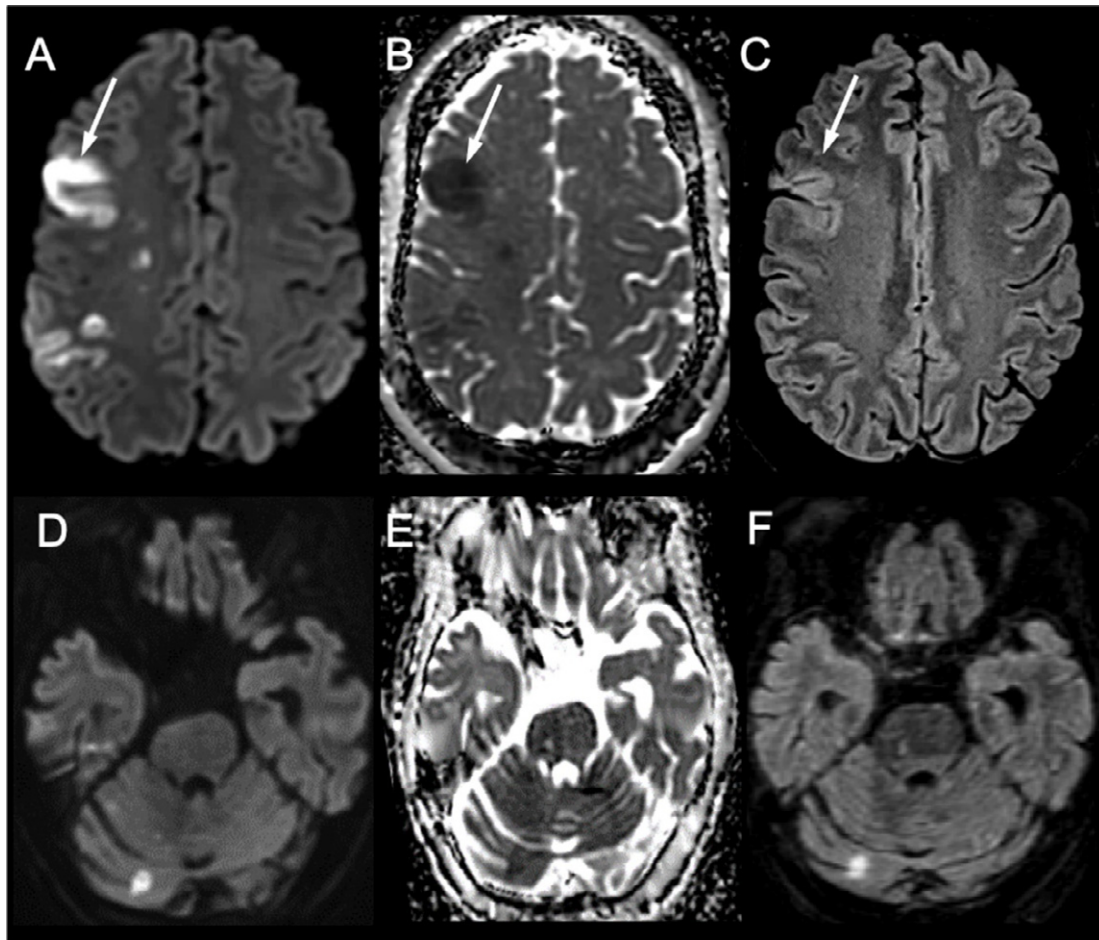


Figure E1: Ischemic infarction. Ischemic infarct in two patients infected with severe acute respiratory syndrome coronavirus 2 in the right superficial territory (patient 1, A-C) and the right cerebellum (patient 2, D-F) visible as areas of high signal on diffusion-weighted imaging (A-D, arrow), with apparent diffusion coefficient decrease (B and E, arrow), with a high signal on FLAIR images (C and F, arrow).

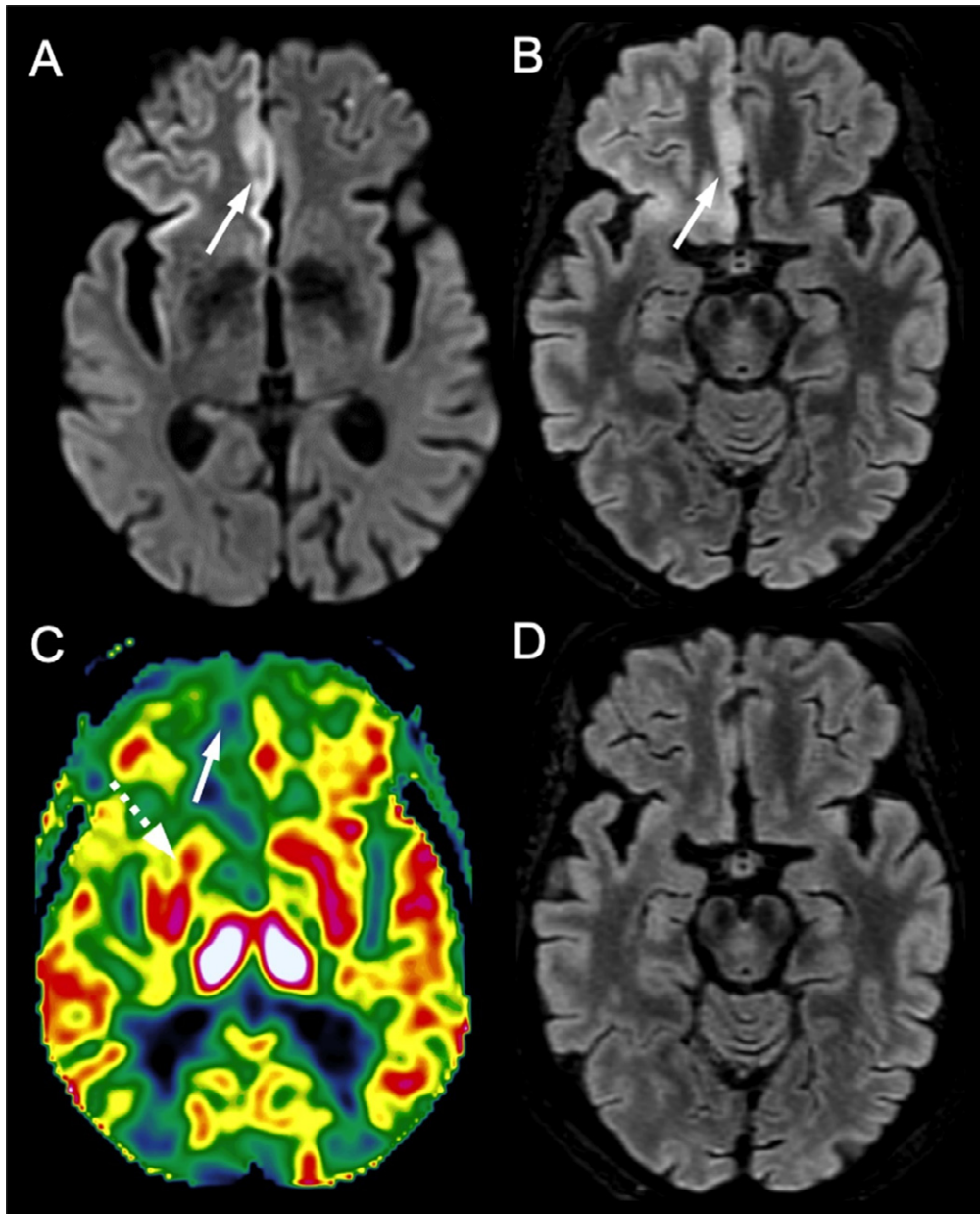


Figure E2: Post-ictal changes. A 69-year-old male in intensive care presenting with status epilepticus after ten days of flu-like symptoms, showing a right cortical frontobasal hyperintensity on diffusion-weighted images (A, arrow) with edema on FLAIR (B, arrow), hypoperfusion on arterial spin labeling perfusion imaging in the cortical (C, arrow) and subcortical (C, dashed arrow) areas. Signal changes disappeared on the follow-up MRI performed 17 days later (D).

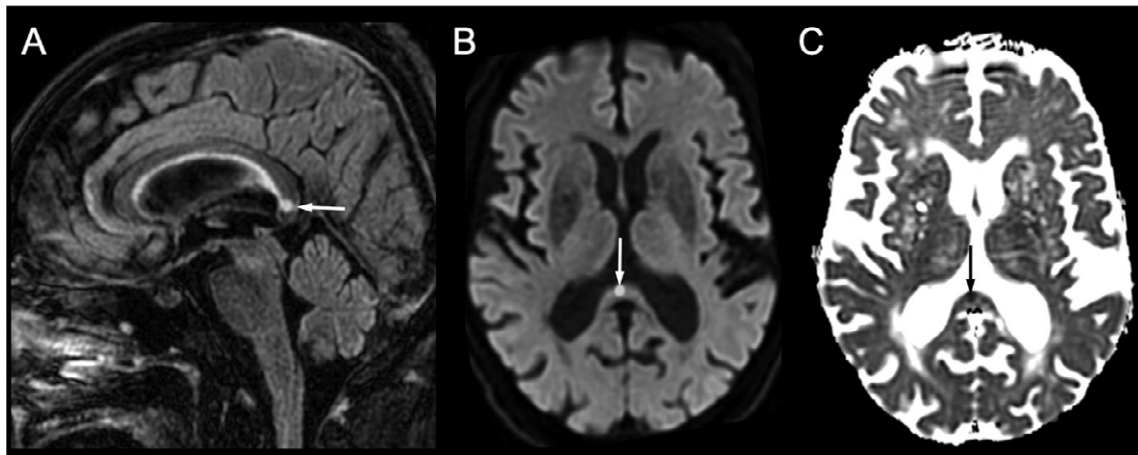


Figure E3: Cytotoxic Lesions of the Corpus Callosum (CLOCC). A 77-year-old male presenting with impaired consciousness and weakness of the left lower limb, who showed a focal lesion in the splenium of the corpus callosum, hyperintense on sagittal FLAIR image (A, arrow) and diffusion-weighted imaging (B, arrow) with decreased apparent diffusion coefficient.

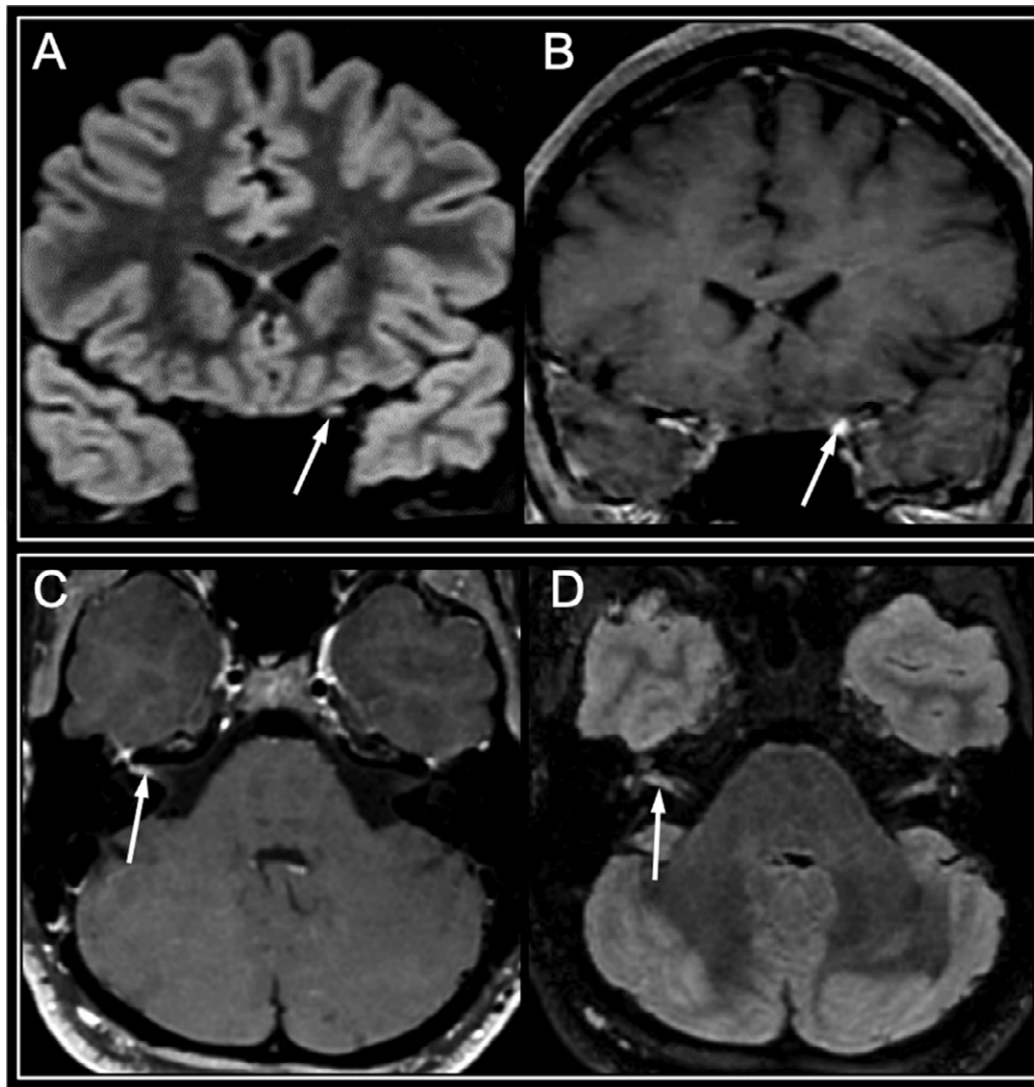


Figure E4: Cranial neuritis. Left optic neuritis in a 28 year-old female presenting with sudden left decreased visual acuity a week after the onset of COVID-19 symptoms (A-C). The intracanalicular segment of the left optic nerve was thickened, with a high signal on coronal FLAIR images (A, arrow), and enhancement on coronal (B, arrow) fat-suppressed post-contrast images. Right vestibulocochlear neuritis in a 31 year-old female presenting with sudden headache, vertigo, vomiting and right hearing loss (C, D). There was enhancement of the right vestibular and cochlear nerve fibers within the internal auditory canal, extending to the geniculate ganglion, on fat-suppressed post-contrast images (D, arrow).

Table E1

	Clinical cohort (n=308)	Patients with <i>de novo</i> neurological symptoms (n=223)	Patients with brain MRI (n=73)
Age (y-o), mean ± SD (range)	61.8±14.9 (21-97)	61.2±15.3 (21-97)	58.5±15.6 (28-96)
Gender, n (%)	198M/110F (64.3/35.7)	146M/77F (64.5/35.5)	48M/25F (65.8/34.2)
Altered consciousness	89 (28.9)	85 (38.1)	39 (53.4)
*Confusion	32 (10.4)	30 (13.5)	10 (13.7)
*Severely impaired consciousness	57 (18.5)	40 (18.9)	29 (39.7)
*Delayed awakening after sedation withdrawal	15 (4.9)	11 (4.9)	7 (9.6)
Seizure	16 (5.2)	13 (5.8)	10 (13.7)
Focal neurological deficit	45 (14.6)	43 (19.3)	31 (42.5)
Headache	33 (10.7)	31 (13.9)	5 (6.8)
Behavioral abnormalities	21 (6.8)	21 (9.4)	4 (5.5)
Anosmia	28 (9.0)	22 (9.9)	4 (5.5)
Visual symptoms	6 (19.5)	6 (2.7)	1 (1.4)
Guillain-Barre syndrome	3 (1.0)	1 (0.004)	1 (1.4)

Main clinical characteristics of the whole clinical cohort (n=308) and in patients with *de novo* acute neurological symptoms, as described in Figure 1.

Table E2

Summary of the main clinical and MRI findings in the four patients with white matter enhancing lesions and the four other patients with basal ganglia abnormalities.

Patient Age/Sex Medical history	Initial presentation	Neurological presentation	MRI findings	Short-term follow-up
37, M Obesity	*SARS-CoV-2 pneumonia with ARDS *Multiple organ failure *Recurrent venous thrombo-embolism with negative thrombophilia tests	*Late awakening following sedation withdrawal	*MRI performed 38 days after first COVID-19 symptoms *White matter enhancing lesions *Hypoxic lesions of basal ganglia *Multiple microhemorrhages (Figure 3)	*No recovery *Death 42 days after brain MRI
50, M Kidney transplantation	*SARS-CoV-2 pneumonia with ARDS *Multiple organ failure	*Late awakening following sedation withdrawal	*MRI performed 39 days after first COVID-19 symptoms *White matter enhancing lesions *Multiple microhemorrhages involving the corpus callosum (Figure 4)	Progressive consciousness recovery with response to orders Sleep behavior disorder Dysexecutive syndrome
50, M Type 2 diabetes mellitus Arterial hypertension Ischemic stroke	*SARS-CoV-2 pneumonia with ARDS *Multiple organ failure	*Late awakening following sedation withdrawal	*MRI performed 65 days after first COVID-19 symptoms *White matter enhancing lesions *Subacute territorial ischemic infarct (Figure 4)	Progressive consciousness recovery with response to orders Pyramidal signs without motor deficit Cognitive impairment
M, 56 Arterial hypertension	*SARS-CoV-2 pneumonia with ARDS *Multiple organ failure	*Late awakening following sedation withdrawal	*MRI performed 54 days after first COVID-19 symptoms *White matter enhancing lesions *Multiple microhemorrhages involving the corpus callosum	Progressive consciousness recovery with response to orders Persistent tetraparesis

			*PRES on a prior MRI *Multiple microhemorrhages	
42, M Untreated chronic lymphocytic leukemia	*SARS-CoV-2 pneumonia with ARDS	*Late awakening following sedation withdrawal Tetraparesis	*MRI performed 47 days after first COVID-19 symptoms *Substantia nigra abnormalities with diffusion restriction and FLAIR hyperintensity *Multiple microhemorrhages involving the corpus callosum (Figure 5)	Progressive consciousness recovery Persistent peripheral motor deficit consistent with ICU-acquired weakness Mild parkinsonian symptoms
56, F Type 2 diabetes mellitus Obesity	*SARS-CoV-2 pneumonia with ARDS *No episode of cardiorespiratory arrest	Late awakening	*MRI performed 48 days after first COVID-19 symptoms *Diffusion restriction and enhancement within the globus pallidus (Figure 5)	No follow-up MRI available
62, F Chronic cardiovascular disease	*SARS-CoV-2 pneumonia with ARDS *Cardiorespiratory arrest * Type 2 diabetes mellitus without any decompensation diagnosed during the hospitalization	Late awakening	*MRI performed 54 days after first COVID-19 symptoms *T1 hyperintensity within the striatonigral pathways (Figure 5)	Progressive consciousness recovery Persistent motor deficit
68, F Type 2 diabetes mellitus Bipolar disorder treated with neuroleptics	*SARS-CoV-2 pneumonia *Decompensated diabetes mellitus *Severe hyponatremia	Hyperosmolar coma	*MRI performed 6 days after first COVID-19 symptoms * Central pontine myelinolysis * T1 hyperintensity within the globus pallidus	Progressive consciousness recovery Post-neuroleptic parkinsonian syndrome

Table E3: Coagulation Tests Findings

Coagulation parameters (normal range)	Patients with 1-4 microhemorrhages (n=12/71) ¹		Patients with ≥5 microhemorrhages (n=8/71) ¹		Patient with a deep cerebral vein thrombosis (n=1/73)
	Non-ICU (n=6/37)	ICU (n=6/34)	Non-ICU (n=1/37)	ICU (n=7/34)	
Platelet count, 10 ⁹ /L (150-400)	266.6±41.0 (211.0-342.0)	357.8±162.4 (86.0-577.0)	235.0	375±135.3 (173-577)	373.0
Prothrombin ratio, (70-120)	87.7±20.3 (50-100)	88.8±9.4 (68.0-100)	100	90.6±6.8 (84-100)	83.0
Partial thromboplastin ratio, (0.8-1.2)	1.2±0.2 (1.1-1.5)	1.3±0.2 (0.9-1.8)	1.3	1.3±0.3 (0.9-1.7)	1.03
Fibrinogen, mg/L (2-4)	5.9±1.0 (4.2-7.0)	5.5±0.7 (3.3-8.2)	6.9	5.6±2.1 (3.3-8.2)	5.5
D-dimers, µg/L (<500)	1538±1351 (470-3870)	1668±1250 (413-3400)	470.0	2404±1724 (413-3400)	— -

Coagulation tests findings in patients with 1 to 4 microhemorrhages (first two columns), in patients with ≥5 microhemorrhages (third and fourth columns) and in the patient with a cerebral deep cerebral vein thrombosis (last column).

Results are expressed in mean ± SD, range

¹ A T2 star or susceptibility-weighted sequence were missing in two patients (one ICU and one non-ICU), explaining the number of 71 (instead of 73).

Abbreviations: ICU: intensive care unit