Retrospective Observational Study of Brain MRI Findings in Patients with Acute SARS-CoV-2 Infection and Neurologic Manifestations

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ORIGINAL RESEARCH • NEURORADIOLOGY

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Conflicts of interest are listed at the end of this article.

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Background: This study provides a detailed imaging assessment in a large series of patients infected with coronavirus disease 2019 (COVID-19) and presenting with neurologic manifestations.

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

Materials and Methods: This was a cross-sectional study conducted between March 23 and May 7, 2020, at the Pitié-Salpêtrière Hospital, a reference center for COVID-19 in the Paris area. Adult patients were included if they had a diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with acute neurologic manifestations and referral for brain MRI. Patients with a prior history of neurologic disease were excluded. The characteristics and frequency of different MRI features were investigated. The findings were analyzed separately in patients in intensive care units (ICUs) and other departments (non-ICU).

Results: During the inclusion period, 1176 patients suspected of having COVID-19 were hospitalized. Of 308 patients with acute neurologic symptoms, 73 met the inclusion criteria and were included (23.7%): thirty-five patients were in the ICU (47.9%) and 38 were not (52.1%). The mean age was 58.5 years ± 15.6 [standard deviation], with a male predominance (65.8% vs 34.2%). Forty-three patients had abnormal MRI findings 2–4 weeks after symptom onset (58.9%), including 17 with acute ischemic infarct (23.3%), one with a deep venous thrombosis (1.4%), eight with multiple microhemorrhages (11.3%), 22 with perfusion abnormalities (47.7%), and three with restricted diffusion foci within the corpus callosum consistent with cytotoxic lesions of the corpus callosum (4.1%). Multifocal white matter–enhancing lesions were seen in four patients in the ICU (5%). Basal ganglia abnormalities were seen in four other patients (5%). Cerebrospinal fluid analyses were negative for SARS-CoV-2 in all patients tested (n = 39).

Conclusion: In addition to cerebrovascular lesions, perfusion abnormalities, cytotoxic lesions of the corpus callosum, and intensive care unit–related complications, we identified two patterns including white matter–enhancing lesions and basal ganglia abnormalities that could be related to severe acute respiratory syndrome coronavirus 2 infection.

Online supplemental material is available for this article.

Since the coronavirus disease 2019 (COVID-19) outbreak in December 2019, there has been growing evidence that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has central nervous system involvement in addition to the primary respiratory target. In a series of 214 patients infected with SARS-CoV-2, more than one-third of patients had neurologic manifestations, such as stroke, seizures, and anosmia (1). Clinical

Abbreviations

CSF = cerebrospinal fluid, COVID-19 = coronavirus disease 2019, EL = encephalitis lethargica, FLAIR = fluid-attenuated inversion recovery, ICU = intensive care unit, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Summary

MRI abnormalities included cerebrovascular lesions, perfusion abnormalities, cytotoxic lesions of the corpus callosum, intensive care unit–related complications, white matter–enhancing lesions, and basal ganglia abnormalities.

Key Results

- Of the 73 patients who presented with neurologic symptoms, 43 (59%) had abnormal MRI findings, including 17 (23%) with acute ischemic infarcts, one (1%) with a deep venous thrombosis, eight (11%) with multiple microhemorrhages, 22 (48%) with perfusion abnormalities, and three (4%) with restricted diffusion foci within the corpus callosum consistent with cytotoxic lesions of the corpus callosum.
- Imaging patterns possibly related to coronavirus disease 2019 were observed in patients in intensive care and included multifocal white matter–enhancing lesions (four patients, 5%) and basal ganglia abnormalities (four patients, 5%).

reports (2–4) and experiments (5,6) from the previous coronavirus epidemics, namely the severe acute respiratory syndrome coronavirus epidemic in 2002 and the Middle East respiratory syndrome epidemic in 2012, have established that coronaviruses have a neurotropic and neuroinvasive potential. Coronaviruses enter the central nervous system using a hematogenous pathway or through the olfactory bulb or peripheral nerves (5,6). In 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 many patients with COVID-19. Proposed pathophysiologic 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 neurologic manifestations admitted for COVID-19 and referred for brain MRI in the Pitié-Salpêtrière Hospital, a reference center for COVID-19. 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 possibly related to COVID-19 when *(a)* they were found in least three patients, *(b)* they were similar across at least three patients, and *(c)* they were not explained by another disease or condition.

Materials and Methods

Study Design and Participants

This study was conducted according to good clinical practice and received approval from the local ethics committee (CER-202028 on April 24, 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. The study was registered on *https://ClinicalTrials.gov* (NCT04362930). Patients referred for brain MRI in the context of COVID-19 between March 23, 2020, and May 7, 2020, were examined in the neuroradiology department of the Pitié-Salpêtrière Hospital, a tertiary neurology center and reference center for COVID-19. The inclusion criteria were as follows: *(a)* diagnosis of SARS-CoV-2 infection via detection of RNA with a nasopharyngeal swab, bronchial aspiration, or bronchoalveolar lavage using reverse transcriptase polymerase chain reaction (RT-PCR) or via chest CT showing results consistent with SARS-CoV-2–associated pneumonia, *(b)* presence of acute neurologic symptoms, *(c)* age greater than 18 years, and *(d)* availability of a brain MRI study. The exclusion criteria were *(a)* underlying progressive central nervous system disease excluding stroke and *(b)* 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, electroencephalograms, 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-T MRI system (Premier; GE Healthcare, Chicago, Ill) with a 48-channel receive head coil. The protocol included three-dimensional T1-weighted (magnetization-prepared rapid acquisition with gradient-recalled echo) and three-dimensional fluid-attenuated inversion recovery (FLAIR) images, susceptibility-weighted imaging, three-dimensional pseudocontinuous arterial spin labeling perfusion imaging, diffusion-weighted imaging, and three-dimensional gadolinium-enhanced spin-echo T1-weighted imaging. In case of suspicion of acute stroke, axial FLAIR sequence, diffusion-weighted imaging, susceptibility-weighted imaging, arterial spin labeling, and arterial three-dimensional time of flight sequences were performed.

Image Analysis

Two neuroradiologists (L.C., N.P.; 7 and 14 years of experience, respectively) independently analyzed all MRI scans. 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; arterial spin labeling perfusion abnormalities; parenchymal and meningeal enhancement; hemorrhages; vessel permeability; cranial nerve abnormalities including thickening; abnormal T2 hyperintensity; and contrast enhancement.

Statistical Analysis

Age was expressed as mean ± standard deviation. Categorical variables were expressed as counts and percentages. Participants were divided into an intensive care unit (ICU) group, includ-

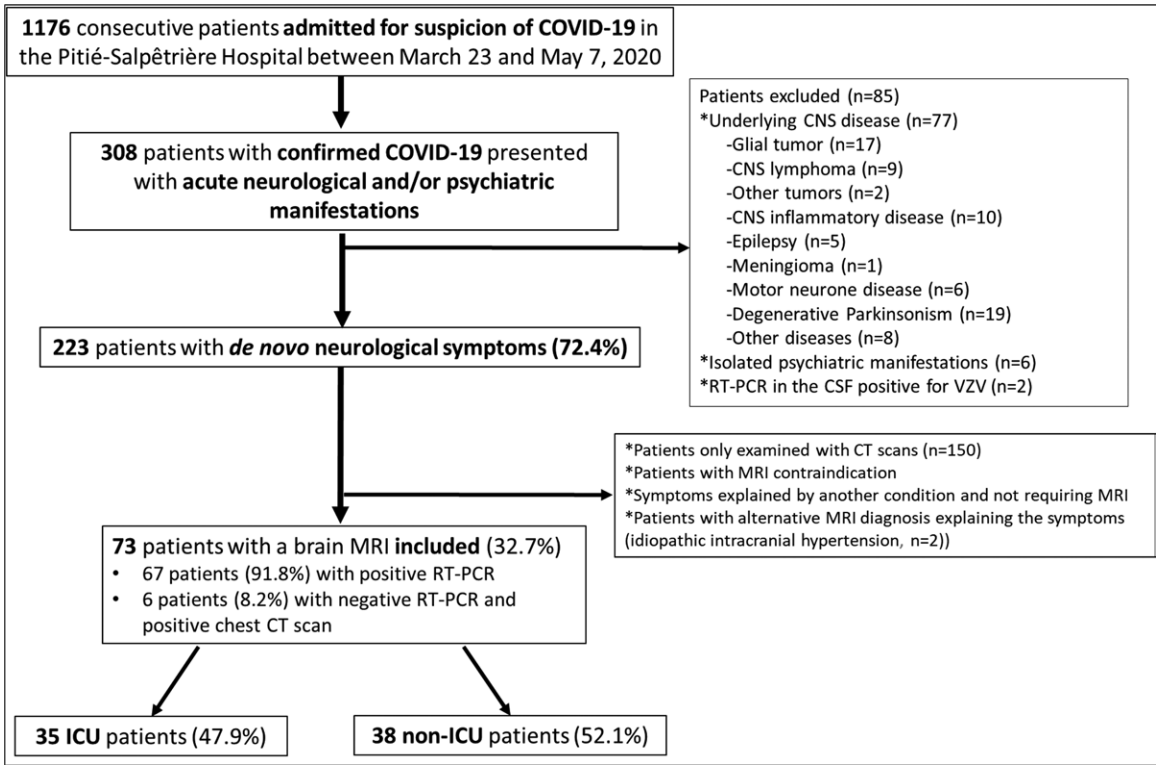

Figure 1: Flowchart of patient inclusion. CNS = central nervous system, COVID-19 = coronavirus disease 2019, CSF = cerebrospinal fluid, ICU = intensive care unit, RT-PCR = reverse transcriptase polymerase chain reaction, VZV = varicella zoster virus.

ing patients hospitalized in an ICU, and a non-ICU group, with patients never hospitalized in an ICU. Age was compared between the groups by using the Student *t* test. Proportions for categorical variables were compared by using the Pearson χ^2 test or Fisher exact test. Statistical analyses were performed with *R* software (version 3.6.1; *www.r-project.org*). The significance threshold was set at $P < .05$.

Results

Patient Recruitment

During the inclusion period, 1176 consecutive patients suspected of having COVID-19 were hospitalized in Pitié-Salpêtrière Hospital. Three hundred eight of these patients (26.2%) presented with neurologic manifestations, psychiatric manifestations, or both, and 223 (72.4%) of these patients had de novo acute neurologic symptoms (ie, no previous history of neurologic disease). Seventy-three patients met the inclusion criteria (73 of 223 [32.7%]). In these 73 patients, RT-PCR test results were positive in 67 (91.8%). In the six remaining patients with negative SARS-CoV-2 RT-PCR test results (8.2%), chest CT scans were highly suggestive of SARS-CoV-2–associated pneumonia. Thirty-five patients were admitted to the ICU (47.9%), and 38 were not (52.1%). The patient flowchart is detailed in Figure 1.

Patient Characteristics

Patient characteristics are summarized in Table 1. The mean age was 58.5 years ± 15.6 (65.8% male), without a difference between patients in the ICU and those who were not. MRI examinations were performed 22.3 days ± 15.7 (range: 0–65 days, significantly longer than in the ICU group; $P < .001$) after the onset of COVID-19 symptoms and 5.9 days ± 6.7 (range, 0–30 days) after the onset of neurologic symptoms. The most frequent neurologic manifestations were impaired consciousness not explained by therapy (39 of 73 [53.4%]), focal neurologic deficit (31 of 73 [42.5%]), and seizure (10 of 73 [13.7%]). Patients in the ICU had significantly more impaired consciousness than those not in the ICU (85.7% vs 23.7%, $P < .001$) but no difference in the rate of seizures or focal deficits. Results of CSF analysis were available for 39 of 73 patients (53.4%) and showed mild pleiocytosis in eight (21.6%), hyperproteinorachia in 10 (28.6%), oligoclonal bands in two (16.7%), and mild increase in interleukin 6 levels in eight (72.7%). For all patients, RT-PCR test results for SARS-CoV-2, herpes simplex viruses 1 and 2, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus, as well as the CSF bacterial culture were negative. Electroencephalogram analysis was available for 40 (54.8%) of 73 patients and showed abnormal findings related to seizure or encephalopathy in nine of these 40 patients (22.5%; two in the non-ICU group, seven in the ICU group) and nonspecific findings in 24 (60.0%; nine in the non-ICU group, 15 in the ICU group). Clinical characteristics of the other nonincluded patients are provided in Table E1 (online).

MRI Findings

MRI examinations revealed no significant abnormalities in 30 patients (22 in the non-ICU group, eight in the ICU group), apart from changes usually seen in elderly patients, and showed abnormal findings in 43 patients (58.9%).

Table 1: Patient Characteristics

Characteristic	Patients with Brain MRI (*n* = 73)	Non-ICU Group (*n* = 38)	ICU Group (*n* = 35)	*P* Value
Age (y)*	58.5 ± 15.6 (28–96)	58.1 ± 18.6 (28–96)	58.9 ± 11.7 (35–78)	.835
Sex				.140
Male	48 (65.8)	22 (57.9)	26 (74.3)	
Female	25 (34.2)	16 (42.1)	9 (25.7)	
Delay of MRI examination from the onset of COVID-19 symptoms (d)*	22.3 ± 15.7 (0–65)	16.1 ± 12.0 (0–50)	28.5 ± 16.9 (0–65)	<.001†
CNS manifestations	69 (94.5)	34 (89.4)	35 (100)	.048†
Altered consciousness	39 (53.4)	9 (23.7)	30 (85.7)	<.001†
Confusion	10 (13.7)	9 (23.7)	0 (0)	.002†
Severely impaired consciousness	17 (23.3)	0 (0)	17 (48.6)	<.001†
Coma	3 (4.1)	0 (0)	6 (17.1)	.007†
Delayed awakening after sedation withdrawal	7 (9.6)	0 (0)	7 (20)	.004†
Focal neurologic deficit	31 (42.5)	17 (36.8)	14 (40.0)	.683
Seizure	10 (13.7)	6 (15.8)	4 (11.4)	.588
Behavioral abnormalities	4 (5.5)	4 (10.5)	…	…
Headache	5 (6.8)	5 (13.2)	…	…
PNS manifestations‡	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§	39/73	19/38	20/35	NA
High white blood cell count (<5/mm^3)	8/37 (21.6)	3/17 (17.6)	5/20 (25.0)	.71
Hyperproteinorachia (<0.40 g/L)	10/35 (28.6)	3/16 (18.8)	7/19 (36.8)	.48
Presence of oligoclonal bands	2/12 (16.7)	2/8 (25.0)	0/4 (0)	>.99
Intrathecal immunoglobulin G synthesis	0/7 (0)	0/3 (0)	0/4 (0)	>.99
Elevated interleukin-6 level	8/11 (72.7)	4/4 (100)	4/7 (57.1)	.66
Elevated interleukin-10 level	0/11 (0)	0/4 (0)	0/7 (0)	>.99
RT-PCR test was positive for SARS-CoV-2	0/36 (0)	0/19 (0)	0/17 (0)	>.99

Note.—Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. CNS = central nervous system, COVID-19 = coronavirus disease 2019, ICU = intensive care unit, PNS = peripheral nervous system, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

* Data are mean ± standard deviation. Data in parentheses are the range.

† $P < .05$.

‡ PNS examination was limited in patients in the ICU because of severely impaired consciousness.

§ The first number is the number of patients with positive findings, and the second is the number of patients with available data. Data in parentheses are percentages.

Seventeen patients had acute ischemic infarct; one, a deep venous thrombosis; eight, multiple microhemorrhages; nine, seizure-related perfusion abnormalities; 10, isolated perfusion abnormalities; four, multifocal-enhancing white matter lesions; three, restricted diffusion foci within the splenium of the corpus callosum; three, hypoxic-ischemic lesions; two, posterior reversible encephalopathy syndrome; three, metabolic abnormalities; and two, neuritis (Table 2). Clinical details for patients with white matter lesions and basal ganglia abnormalities are presented in Table E2 (online).

Cerebrovascular Complications

Stroke.—Twelve of the 17 patients with acute ischemic infarct (70.6%) had multiple ischemic foci, whereas eight (47.0%) had a territorial infarction (Fig E1 [online]). Three patients had both types of lesions. There was no significant difference between the non-ICU and ICU groups ($P = .638$).

Deep cerebral vein thrombosis.—Extensive deep cerebral venous thrombosis complicated by hemorrhagic venous infarction was diagnosed in a 72-year-old man in the ICU without known risk factors for thrombosis and with normal baseline coagulation test results (Table E3 [online]).

Microhemorrhages.—Patients in the ICU had more multiple microhemorrhages (five or more) than did those not in the ICU (20.6% vs 2.7%, $P = .017$), and these involved the corpus callosum in five patients (Fig 2). Patients with microhemorrhages tended to have increased partial thromboplastin time because of

Table 2: Patient MRI Findings

MRI Finding	Total (n = 73)	Non-ICU (n = 38)	ICU (n = 35)	P Value
Ischemic lesions*	17 (23.3)	8 (21.1)	9 (25.7)	.638
Territorial arterial infarct	8 (11.0)	4 (10.5)	4 (11.4)	.902
Ischemic spots	12 (16.4)	4 (10.5)	8 (22.9)	.156
Cerebral venous thrombosis	1/73 (1.4)	0/38 (0)	1/35 (2.9)	.294
Microhemorrhages†	20/71 (28.2)	7/37 (18.9)	13/34 (38.2)	.071
0	50 (70.4)	29 (78.4)	21 (61.8)	.126
≥5	8 (11.3)	1 (2.7)	7 (20.6)	.017‡
Involvement of the corpus callosum	5/71 (7.0)	0 (0)	5 (14.7)	.016‡
Patients with ≥5 microhemorrhages on ECMO	2/8 (25.0)	….	2 (28.6)	…
Perfusion abnormalities§	22/46 (47.8)	7/22 (31.8)	15/24 (62.5)	.037‡
Seizure related	9 (19.6)	4 (18.2)	5 (20.8)	.821
Secondary to ischemic lesions	4 (8.7)	1 (4.5)	3 (12.5)	.339
Isolated	10 (21.7)	2 (9.1)	8 (33.3)	.046‡
Multifocal white matter lesions	4/73 (5.5)	0/38 (0)	4/35 (16.7)	.032‡
Basal ganglia lesions	4/73 (5.5)	0/38 (0)	4/35 (16.7)	.032‡
Substantia nigra	1 (1.4)	0 (0)	1 (2.9)	.294
Globus pallidus	2 (4.8)	0 (0)	2 (9.5)	.147
Striatonigral pathway	1 (1.4)	0 (0)	1 (2.9)	.294
CLOCC‖	3/73 (4.1)	1/38 (2.6)	2/35 (5.7)	.507
PRES	2/73 (2.7)	0/38 (0)	2/35 (5.7)	.135
Hypoxic-ischemic lesions	3/73 (4.1)	0/38 (0)	3/35 (8.6)	.065
Central pontine myelinolysis	3/73 (4.1)	0/38 (0)	3/35 (8.6)	.135
Meningeal enhancement#	2/42 (4.8)	0/21 (0)	2/21 (9.5)	.147
Corticospinal tracts FLAIR hyperintensity	1/73 (1.4)	0/38 (0)	1/35 (2.9)	.135
Neuritis**	2/73 (2.7)	2/38 (5.3)	0/35 (0)	.169

Note.—Unless otherwise indicated, data are numbers of patients. When two numbers are separated by a virgule, the first number is the number of patients with positive findings, and the second is the number of patients with available data. Data in parentheses are percentages. The characteristics of the microhemorrhages were consistent with cerebral amyloid angiopathy in one patient in the non-ICU group. CLOCC = cytotoxic lesions of the corpus callosum, 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.

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

† No susceptibility- or T2*-weighted sequence was available in one patient in the non-ICU group and one in the ICU group.

‡ $P < .05$.

§ Arterial spin labeling was available and interpretable in 46 participants including 22 patients in the non-ICU group and 24 patients in the ICU group. In two patients, perfusion abnormalities could be attributed to both seizure and ischemia.

‖ Enhancement of the corpus callosum signal abnormality spot was seen in one patient; no contrast material was administered in the two other patients. They were potentially related to leukostasis in a patient with chronic lymphocytic leukemia in the ICU.

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

** Including optic neuritis and vestibulocochlear neuritis.

preventive anticoagulation therapy (Table E3 [online]). Anticoagulation overdose occurred in one patient in the ICU. Two patients in the ICU with multiple microhemorrhages (28.6%) had extracorporeal membrane oxygenation.

Perfusion Abnormalities

Twenty-two of 46 patients (47.8%) had perfusion abnormalities that were related to seizure in nine patients (19.6%) and 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. Patients in the ICU had more perfusion abnormalities than did patients not in the ICU (62.5% vs 31.8%, $P = .037$), with a higher rate of isolated perfusion abnormalities (33.3% vs 9.1%, $P = .046$). In particular, marked postictal changes associating edema and diffusion restriction within the right frontobasal cortex were observed in a 69-year-old patient in the ICU who presented with status epilepticus (Fig E2 [online]).

White Matter–enhancing Lesions

Four patients in the ICU 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 (Figs 3, 4).

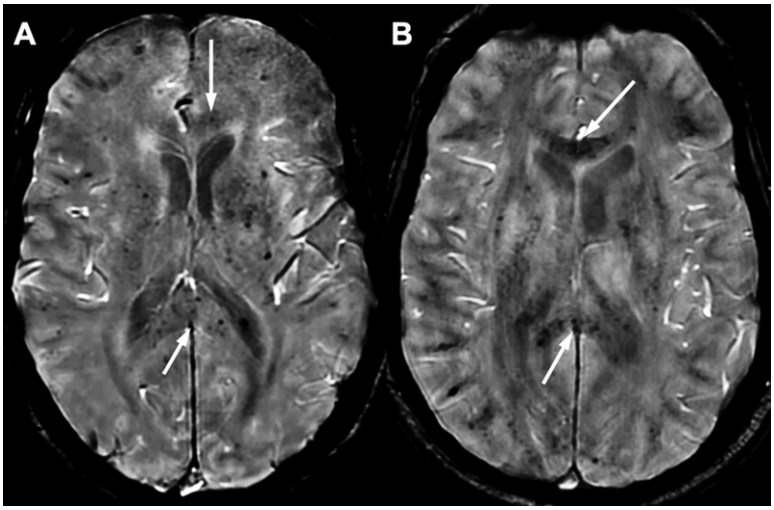

Figure 2: Microhemorrhages. Diffuse microhemorrhages involving the corpus callosum in two patients in the intensive care unit, *A*, receiving extracorporeal membrane oxygenation (EMCO) (arrows) and, *B*, not receiving ECMO (arrows).

Basal Ganglia Abnormalities

Basal ganglia abnormalities were seen in four other patients in the ICU 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 (Fig 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 material administration was not performed). In one case, diffusion imaging results were normal on the follow-up MRI scans obtained 25 days later. Follow-up MRI was not performed in the other two patients. This aspect suggested cytotoxic lesions of the corpus callosum (Fig E3 [online]).

Posterior Reversible Encephalopathy Syndrome

Typical findings of posterior reversible encephalopathy syndrome with parieto-occipital and superior frontal swelling reversible on the follow-up MRI were detected in one patient in the ICU group. Reversible swelling involving the midbrain and basal ganglia, also consistent with posterior reversible encephalopathy syndrome, was seen in another patient in the ICU group with multiple organ failures (Fig 6).

Hypoxic-Ischemic Lesions

Hypoxic-ischemic lesions were seen in three patients in the ICU group with a history of cardiopulmonary arrest (n = 1) or severe low flow (n = 2).

Metabolic Changes

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

Meningeal Enhancement

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

Discussion

Neuroimaging examinations performed 2–4 weeks after symptom onset in 73 patients with coronavirus disease 2019 with acute de novo neurologic manifestations showed ischemic lesions, diffuse microhemorrhages involving the corpus callosum, deep vein thrombosis, perfusion abnormalities, cytotoxic lesions of the corpus callosum, and other intensive care unit–related complications, as well as two other patterns that include 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 findings seen with acute disseminated encephalomyelitis, in which lesions tend to be asymmetric, 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 *(a)* the periventricular topography of lesions, *(b)* their morphology associating an oval shape and ill-defined margins, and *(c)* the perivascular distribution of enhancement. This latter feature has been described in vasculopathies, such as posterior reversible encephalopathy syndrome and Susac syndrome, and in disorders with angiocentric infiltrates, especially in neurolupus and neurosarcoidosis (19) and in cluster of differentiation-8 (CD-8) encephalitis in patients with HIV (20). Similarly, the pattern of white matter–enhancing lesions in our study could somehow reflect a vasculitislike phenomenon or an inflammatory disorder with angiocentric involvement (19,20). This pattern has also been observed in a recent study (9), reinforcing the hypothesis of 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 have 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

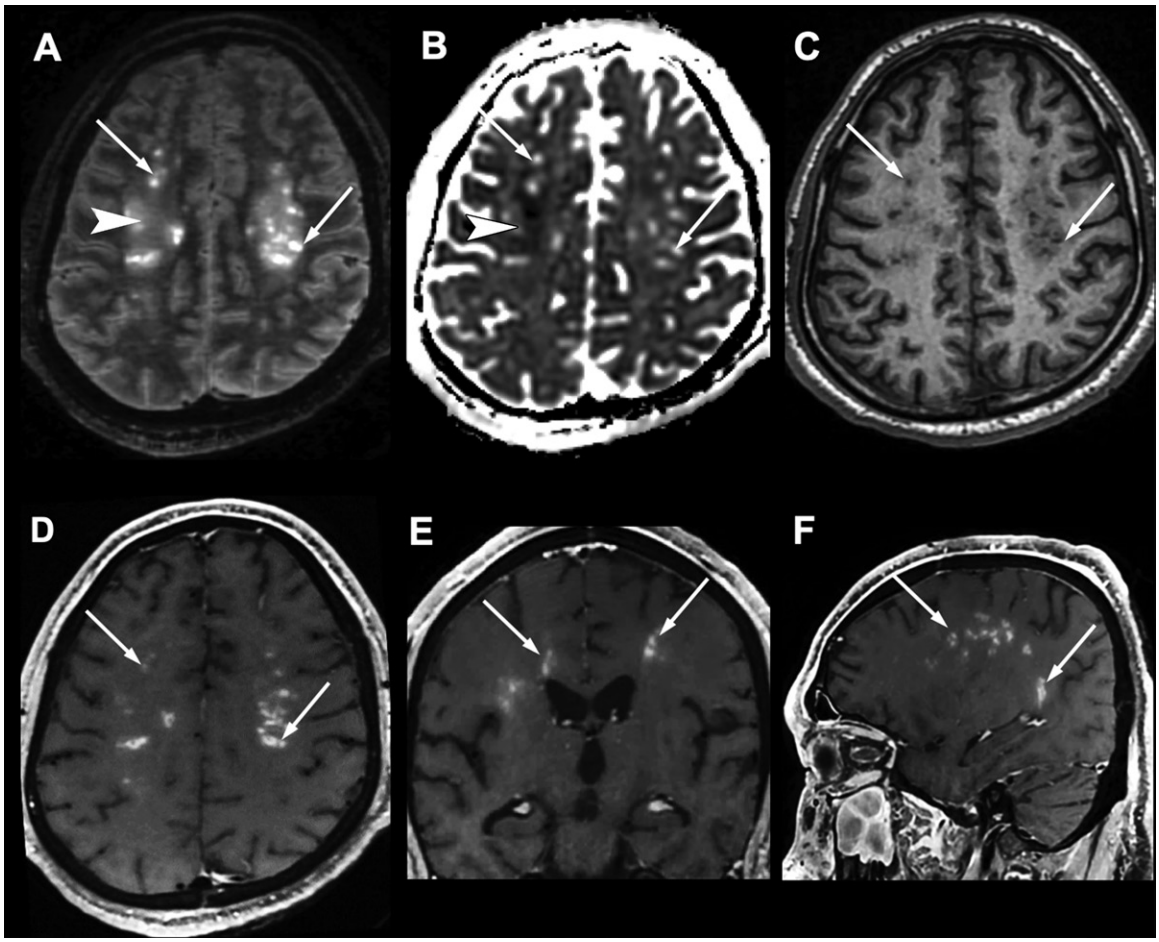

Figure 3: White matter–enhancing lesions in a 37-year-old obese man with no relevant medical history who was admitted to the intensive care unit for severe acute respiratory syndrome coronavirus 2–associated pneumonia 10 days after the onset of flulike symptoms. He developed severe acute respiratory syndrome, recurrent venous thromboembolism with negative thrombophilia test results, and multiorgan failure. MRI was performed for late awakening after withdrawal of sedation after 38 days of intensive care. The patient did not recover consciousness and died 42 days after brain MRI. There were symmetrical multifocal periventricular and deep white matter lesions that were hyperintense on axial fluid-attenuated inversion recovery (FLAIR) images, *A*, with a vacuolated appearance (arrows), *B*, without diffusion restriction (arrows), *C*, that were hypointense on T1-weighted images (arrows), *D–F*, and with perivascular enhancement on postcontrast T1-weighted images (arrows). These lesions were associated with white matter FLAIR hyperintensities (arrowhead in *A*) with decreased apparent coefficient diffusion (arrowhead in *B*).

fatal outcome in about one-third of patients. Delayed parkinsonism and neuropsychiatric signs may occur (22). Neuropathologic 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 origin of EL is still unknown, infectious and environmental causes have been proposed (24). More recently, examination of archived brain material did not show influenza RNA, whereas the presence of oligoclonal bands in the CSF and the efficacy of corticosteroids suggested that EL might be an immune-mediated condition (23). Follow-up of the patients with basal ganglia abnormalities from 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, as SARS-CoV-2 RT-PCR tests of CSF yielded negative findings in all tested patients. However, a relationship with COVID-19 appears possible since these lesions were similarly observed in several patients and were not explained by another disease or condition. To date, SARS-CoV-2 RNA has been found in the CSF of only three patients (9,26,27). Several hypotheses could be formulated to explain negative RT-PCR test results 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 contrast material administration (the meningeal contrast enhancement in other cases was reported mainly on postcontrast FLAIR images). It could also reflect a lack of meningeal involvement in our series, considering that SARS-CoV-2 could have an intraneuronal localization, as reported with severe acute respiratory syndrome coronavirus (28). Second, indirect viral pathogenesis through an immune-mediated mechanism, a systemic inflammatory response syndrome, or both could be involved. Such an immune process could also explain the occurrence of neuritis or Guillain-Barré syndrome

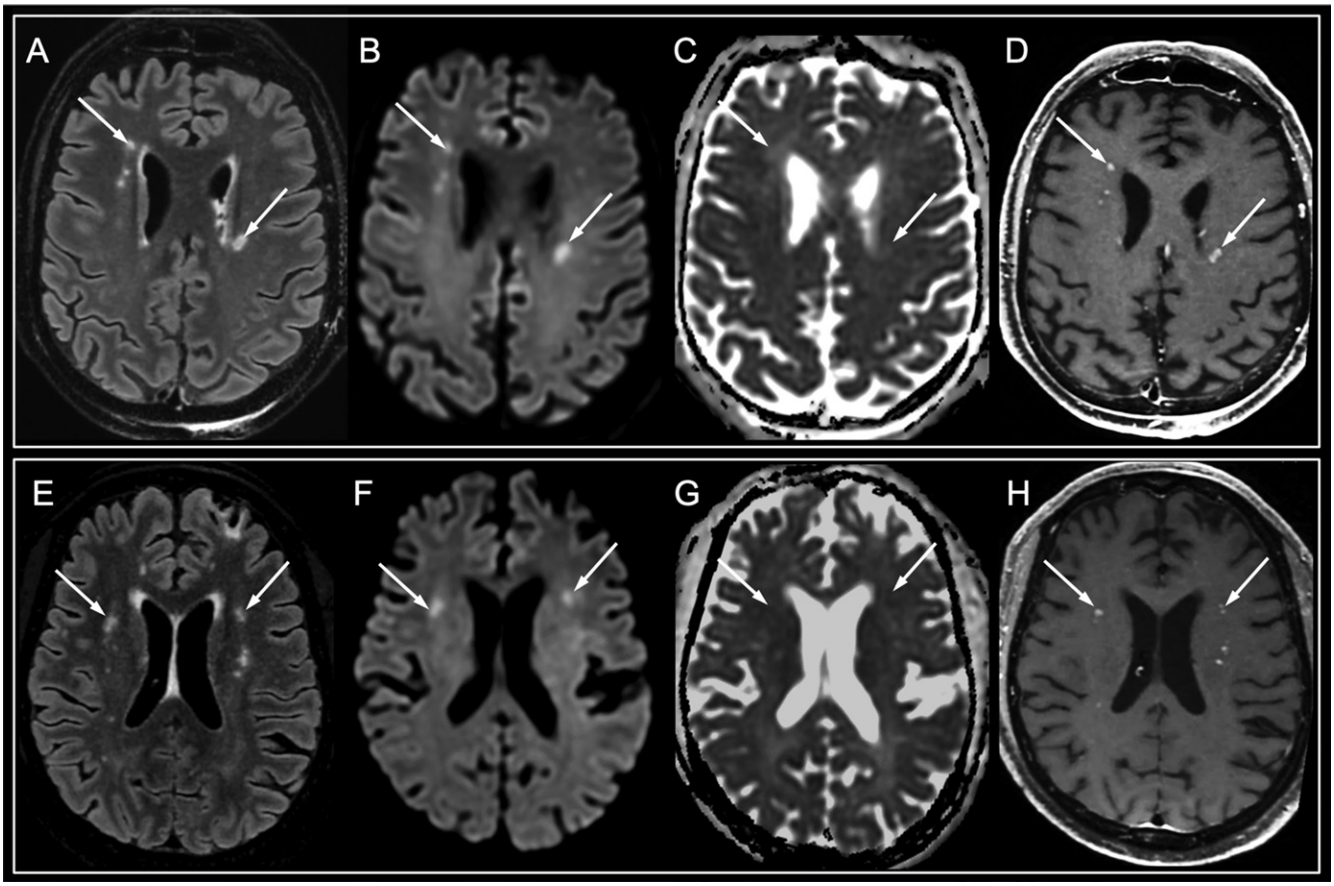

Figure 4: White matter–enhancing lesions in, *A–D*, a 50-year-old man with a history of kidney transplantation and, *E–H*, a 50-year-old man in the intensive care unit with type 2 diabetes. These patients experienced late awakening after withdrawal of sedation after 39 and 65 days, respectively, of intensive care for severe hypoxic severe acute respiratory syndrome coronavirus 2–associated pneumonia complicated by severe acute respiratory syndrome. Both patients progressively recovered consciousness and were able to respond to orders. A similar imaging pattern as that in Figure 3 was seen but with fewer white matter lesions appearing hyperintense on fluid-attenuated inversion recovery images (arrows in *A* and *E*,) and diffusion-weighted images (arrows in *B* and *F*), without apparent diffusion coefficient decrease (arrows in *C* and *G*), and with perivascular enhancement on postcontrast T1-weighted images (arrows in *D* and *H*).

(29). Third, the delay between the RT-PCR assay and the stage of infection could also account for the negative results. Brain damage may also result from a first step of central nervous system viral replication followed by an immune-mediated phenomenon (5,7) in which the virus is no longer detectable, as supported by the relatively long delay between the first respiratory symptoms and the neurologic impairment in our study. Postmortem neuropathologic examinations in 18 patients with COVID-19 showed only hypoxic changes, without signs of encephalitis (30). Viral RNA was detected at low levels, possibly due to in situ viral RNA from the bloodstream (30). Another neuropathologic 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 central nervous system 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 extracorporeal membrane oxygenation (33). Microhemorrhages could be explained by the presence of extracorporeal membrane oxygenation in two 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 in our series. It is now recognized that seriously ill patients with COVID-19 have higher risk for venous and arterial thromboembolic events (34–36), despite prophylactic or curative anticoagulation, as compared with matched patients without COVID-19 (35). The higher percentage in our series compared with previous series (14,37) can 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 to enter cells, a receptor that is expressed in the epithelia of the lungs and small intestine and is 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 phenomenon, with a massive inflammatory cascade, may lead to endothelial damage, resulting in stroke, thrombosis, and hemorrhage (38).

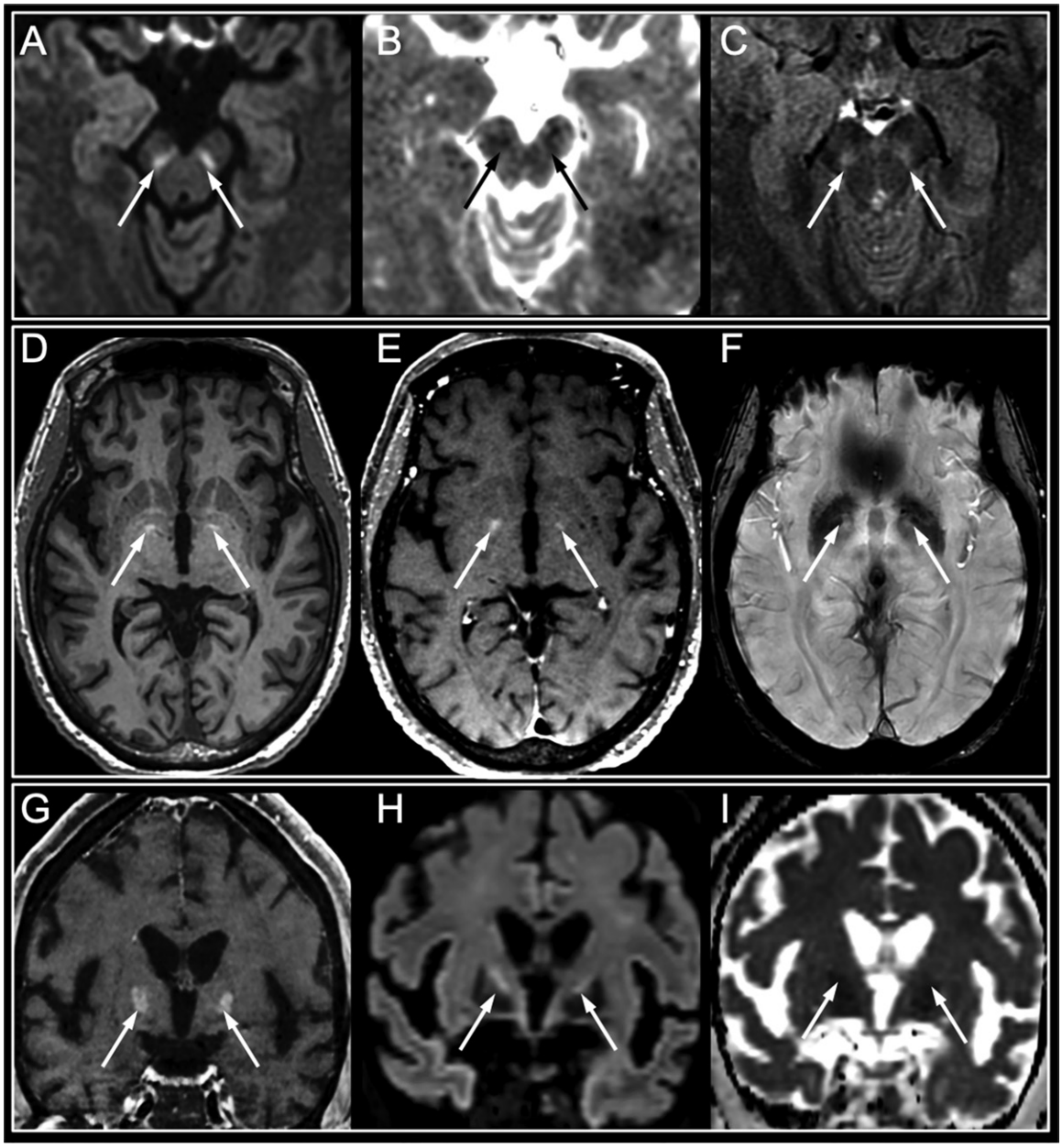

Figure 5: Basal ganglia abnormalities in three patients who experienced late awakening after withdrawal of sedation in the context of severe acute respiratory syndrome coronavirus 2 hypoxic pneumonia with severe acute respiratory syndrome. *A–C,* Images in a 42-year-old man with untreated chronic lymphocytic leukemia who had tetraparesis upon awakening after 47 days of intensive care. Hyperintensity within the substantia nigra on a diffusion-weighted image (arrows in *A*) with decreased apparent diffusion coefficient (arrows in *B*) and hyperintensity on axial fluid-attenuated inversion recovery images (arrows in *C*) were visible. The follow-up neurologic examination showed complete consciousness recovery with persistent peripheral motor deficit consistent and mild parkinsonian symptoms. *D–F,* Images in a 62-year-old woman with diabetes and chronic cardiovascular disease who experienced cardiorespiratory arrest after 54 days of intensive care. Hyperintensity on precontrast magnetization-prepared rapid acquisition with gradient-recalled echo axial T1-weighted images in the globus pallidus (arrows in *D*) with no enhancement on postcontrast T1-weighted images (arrows in *E*) or hypointensity on susceptibility-weighted images (arrows in *F*). The follow-up neurologic examination also showed complete consciousness recovery with a persistent motor deficit. *G–I,* Images in a 56-year-old woman with diabetes and obesity who experienced late awakening after 48 days of intensive care. Bilateral enhancement within the globus pallidus on coronal postcontrast T1-weighted images (arrows in *G*), with hyperintensity on diffusion-weighted images (arrows in *H*), and decreased apparent diffusion coefficient (arrows in *I*). No follow-up was available.

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 patients with COVID-19: 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 had several limitations. First, clinical examination was limited in this context, and CSF data were available in only

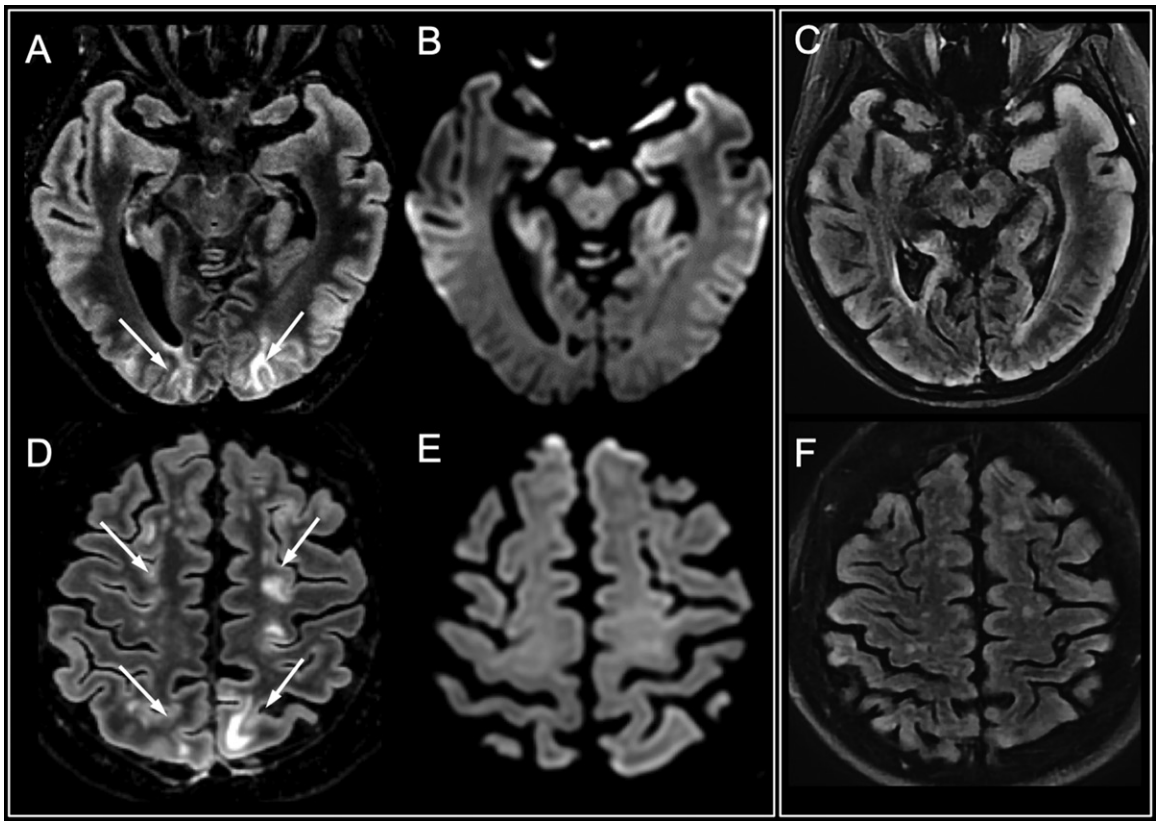

Figure 6: Posterior reversible encephalopathy syndrome. A 66-year-old man infected with severe acute respiratory syndrome coronavirus 2 presented with status epilepticus in the context of pneumonia and severe hyponatremia. *A, D,* Corticosubcortical signal abnormalities in the parieto-occipital and superior frontal regions on fluid-attenuated inversion recovery images (arrows), with, *B* and *E,* no diffusion restriction. *C* and *F,* Follow-up MRI performed 10 days later showed complete disappearance of the lesions.

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 pathologic data with patient outcome will be the scope of future studies.

This study provides a detailed description of neuroimaging findings in a series of patients with coronavirus disease 2019 (COVID-19). In addition to cerebrovascular thrombotic events, perfusion abnormalities, cytotoxic lesions of the corpus callosum, microhemorrhages involving the splenium of corpus callosum, and intensive care unit–related disorders, two MRI patterns were identified: *(a)* white matter lesions with perivascular enhancement, which may reflect vasculitis lesions, inflammatory lesions with angiocentric involvement, or both and *(b)* basal ganglia abnormalities, including substantia nigra involvement. Future studies correlating clinical, imaging, and pathology findings will help determine whether there is a causal relationship between COVID-19 and brain MRI lesions. Longitudinal monitoring will also be necessary to assess the long-term neurologic impact of COVID-19.

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