Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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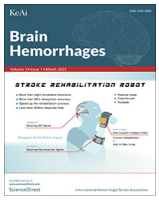

Case Report

Severe stroke in patients admitted to intensive care unit after COVID-19 infection: Pictorial essay of a case series

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ABSTRACT

Patients infected by COVID-19 could require intensive care unit admission especially due to acute respiratory failure. However, neurological manifestations are very common. Among these, ischemic stroke or cerebral hemorrhage may have unfavorable outcome. The mechanisms leading to cerebral damage by SARS-CoV2 are still under debate. One of the most accepted theories implies an endothelial activation which in turns increase the risk of thrombus formation with the development of stroke, either ischemic or hemorrhagic. The more severe the COVID-19 disease, the higher the risk of stroke. Stroke in ICU patients are not frequent, but cerebral hemorrhage has devastating effects with high mortality. In these pictorial essay of case reports, main clinical aspects are discussed, along with a summary of the evidence about pathophysiology and treatment of these patients.

1. Introduction

COVID-19 started at the end of 2019 in Wuhan, China, and then spread worldwide. There have been many waves of infections. At the time of writing, some countries are experiencing a fifth.[1]

The COVID-19 pandemic has put national health systems under stress, especially in terms of patient admittance, mostly for severe cases requiring intensive care unit (ICU) beds.[2] Unfortunately, ICU bed availability has not always been able to meet demand, leading to unintentional deaths outside ICUs.[3]

The reason for ICU admittance for COVID-19 patients is severe acute respiratory failure. Neurological involvement has been frequently reported, however, the main symptoms of which are anosmia, dysgeusia, headache, mental confusion and seizures.[4]

Stroke is another cerebral complication of COVID-19, placing patients at risk of loss of life. The treatment of stroke complications also entails some logistical aspects, such as a dedicated COVID-team.[5]

Neurological manifestations of COVID-19 have been extensively studied, and various theories have been put forward to explain the behavioral changes.[6]

In the ICU, patients with severe acute respiratory failure require sedation for mechanical ventilation. Neurological evaluation thus becomes difficult, especially for deeply sedated patients, with the consequence that some neurological signs and symptoms can be missed.[7]

Critical care physicians have seen an increase in the number of patients with acute stroke related to severe COVID-19 infection [8]. These should be taken into consideration as long as the COVID-19 pandemic continues, not only in patients with a severe manifestation of viral infection but also in those experiencing mild SARS-CoV2 symptoms.[9]

This pictorial review presents five case reports describing the different possible manifestations of stroke in critically ill patients infected with SARS-CoV2, diagnosed with real-time PCR on nasopharyngeal swabs. A summary of the main pathophysiological and treatment aspects is also provided.

Table 1 summarizes the main features of the case reports.

Since only anonymous data are included in this work, the requirement for an Ethics Committee was waived. General informed consent for publication was obtained whenever possible.

2. Case report #1

A 45-year-old woman was admitted to the emergency department (ED) of a spoke center due to disartria. She had been complaining of headaches in the previous days. Forty-two days prior

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Table 1
Clinical characteristics of case reports.

	CASE #1	CASE #2	CASE #3	CASE #4	CASE #5
Age	45	55	61	46	52
Sex	Female	Male	Male	Male	Male
Days from 1st COVID-19 positive test to ICU	42	45	23	1	1
COVID-19 disease severity according to WHO	Mild	Mild	Critical	Mild	Mild
Main symptoms	Headhache	Headhache, nausea, diplopia, postural instability	NA	Left hemiplegia and headhache	Coma
GCS in ED	15	15	NA	11	4
CT scan findings	CVT thrombosis and right fronto-parietal small hemorragic foci	right vertebral and basilar thrombosis	large stroke due to middle cerebral artery thrombosis without any sign of bleeding	large right nucleo-capsular hemorrhage with mass effect on the brain	hyperdensity in the basal cistern with slight prevalence on the right side suggesting subarachnoid hemorrhage
WBC/μL	11,440	13,210	7530	8830	7020
Ly/μL	800	2390	1000	370	1420
PLT/μL	231,000	241,000	328,000	98,000	167,000
CRP mg/dL	170.83	2.55	40.76	8.81	9.02
IL-6 pg/mL	//	//	19		42
aPTT ratio	0.97	0.81	1.25	1.18	1.04
INR	1.08	1.08	1.31	1.10	1.04
D-dimer FEU ng/mL	6242	//	//	1702	40,729
Outcome	Returned home with disability	Died	Returned home with disability	Died	Died

Legend: WBC = white blood cell, Ly = lymphocytes, PLT = platelets, CRP = C-reactive protein, IL-6 = interleukin 6.

to hospital admittance, she had tested positive for COVID-19 (real-time PCR nasal swab) and had suffered a mild case of anosmia. Her past medical history was unremarkable.

An immediate head computed tomography (CT) scan revealed cerebral venous thrombosis with a small hemorrhagic focus in the left temporal lobe (Fig. 1A–B–C). She was then transferred to the hub center where she underwent endotracheal intubation due to her reduced level of consciousness. In the meantime, unfractioned heparin infusion was commenced as the first line treatment. She was also given mannitol as an anti-edema therapy. After 24 h, a control CT scan demonstrated increased signs of intracranial hypertension. Following a multidisciplinary discussion between a neurologist, a neurosurgeon and a critical care physician, it was decided to monitor intracranial pressure with an intraparenchymal probe. This did not reveal any intracranial hypertension, and was removed after five days.

After four days of unfractioned heparin, the patient's therapy was switched to enoxaparin 6000 international units (IU) every 12 h. At day 12, a tracheostomy was performed due to the slow recovery of consciousness and a concomitant need for mechanical ventilation for ventilator-associated pneumonia.

The patient was transferred to the neurology unit at day 20, and to a rehabilitation unit at day 36. She was finally discharged at day 78 with mild neurological deficits including expressive aphasia and partial epilepsy with clonic hemifacial spasms. Chronic medications included levetiracetam 1500 mg bid and warfarin.

3. Case report #2

A 55-year-old man with a history of arterial hypertension and psoriasis was admitted to the ED due to worsening headache, nausea, diplopia and postural instability. Glasgow coma scale was measured at 15. Forty-five days prior to this visit, the patient presented with a mild COVID-19 infection (cold-like symptoms with no respiratory involvement).

An immediate CT head scan revealed a basilar thrombosis (Fig. 2A–B). The patient underwent an angiographic endovascular procedure that reperfused the arterial vessels. However, partial thrombosis at the vertebra-basilar junction persisted. The onset of sudden coma (GCS 3 immediately following angiography) meant that the patient required intubation and mechanical ventilation. He was admitted to the ICU.

After 24 h, a CT-scan revealed a large cerebellar ischemia and hypodensity at the level of the brainstem and thalami. After seven days, the patient was declared brain dead.

4. Case report #3

A 61-year-old man was admitted to the ICU with severe acute COVID-19-related respiratory failure requiring intubation and mechanical ventilation. His medical records included a history of arterial hypertension treated with amlodipine 10 mg once a day.

A CT chest scan revealed severe lung injury caused by COVID-19 infection and pulmonary embolism. Enoxaparin 4000 bid was commenced.

Mechanical ventilation with deep sedation with muscular paralysis lasted for 12 days due to severe gas exchange impairment. Tracheostomy was performed after this, but sedation continued due to severe refractory hypoxemia. At day 14, sedation was gently withdrawn and neurological evaluation revealed a left hemysindrome. An immediate head CT scan revealed a large stroke due to middle cerebral artery thrombosis, without any sign of bleeding (Fig. 3). Antiplatelet therapy was commenced. At day 18, the patient was able to breathe without respiratory support,

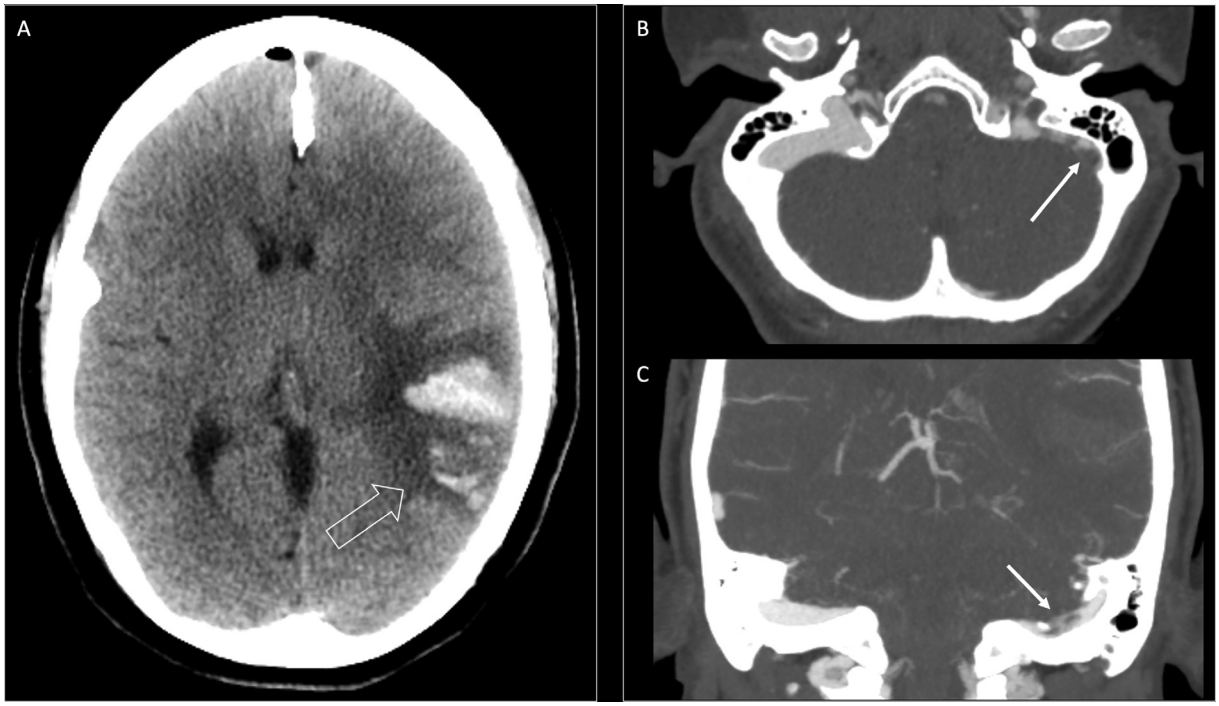

Fig. 1. Axial non-enhanced computed tomography (NECT) showing a large and superficial hemorrhagic infarct involving the left temporal lobe (empty arrow in panel A). The axial and coronal reconstruction of the subsequent CT venography (CTV) examination revealed the presence of different filling defects inside the sigmoid sinus of the same side suggestive for dural sinus thrombosis (arrows in panel B and C).

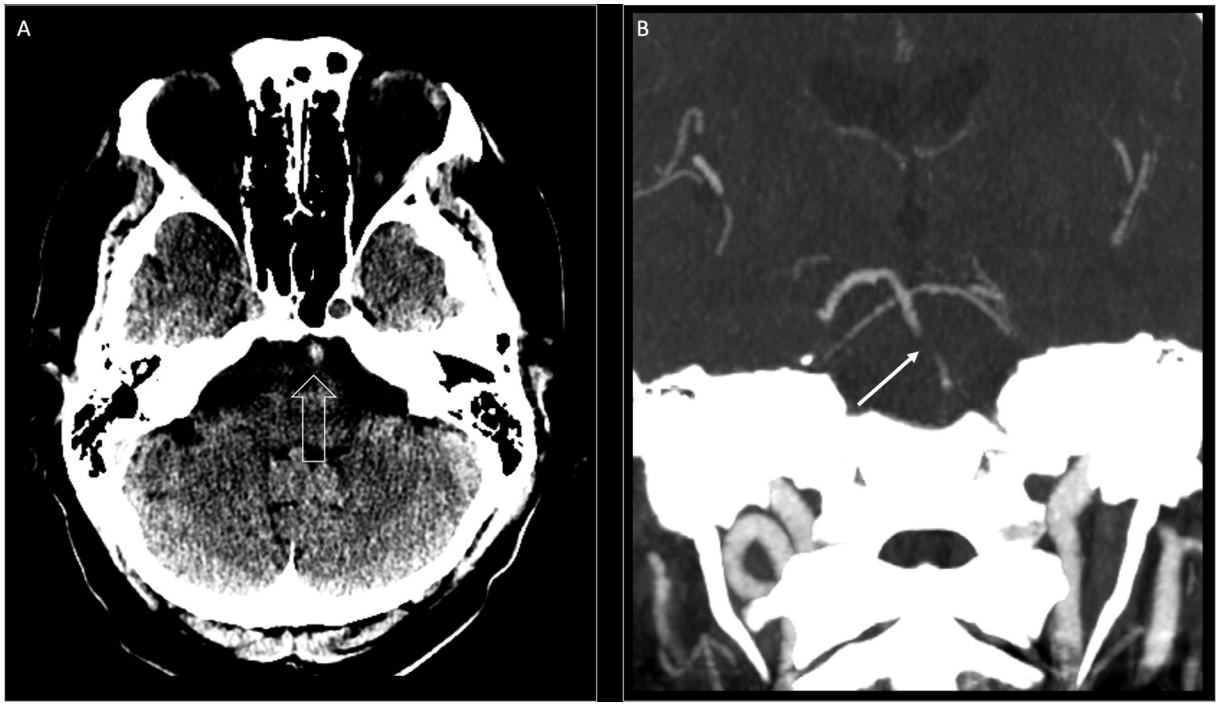

Fig. 2. Axial NECT shows the "dense" artery sign in acute thrombosis of the basilar trunk (empty arrow, panel A) which is not visible and opacified (white arrow in panel B) in the coronal maximum intensity projection reconstruction of CT angiography (CTA) examination.

and at day 20 he was transferred to the neurology unit. Finally, at day 37, he was transferred to the general medicine ward, from where he was discharged to the rehabilitation unit. Neurological examination at hospital discharge revealed mild dysarthria, left facial paralysis (House Brackmann grade 3), plegia of the left arm and weakness of the left leg.

5. Case report #4

A previously healthy 46-year-old man was admitted to the ED due to the sudden onset of left hemiplegia after a headache. The patient tested positive for COVID-19. During admission, GCS decreased rapidly from 15 to 11. He was hence intubated and

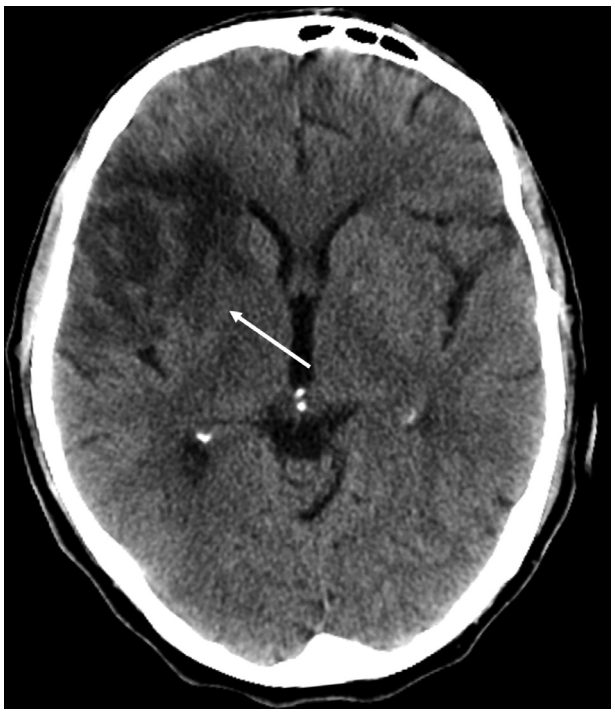

Fig. 3. Axial NECT demonstrating a wedge-shaped hypodense ischemic lesion involving gray - white matter of frontal and insular region of the right cerebral hemisphere (white arrow).

underwent a CT scan that showed a large right nucleo-capsular hemorrhage with mass effect on the brain (Fig. 4A). No surgical treatment was possible.

Blood exams revealed concomitant acute kidney injury (serum creatinine 6.33 mg/dL, blood urea nitrogen 63 mg/dL) and 3.5% of schistocytes and mild thrombocytopenia. Clinicians investigated whether uremic-hemolytic syndrome was the cause. The results of all tests performed (autoantibodies, microbiological and cultural samples) were negative.

After two days, transcranial coded color doppler (TCCD) at the bedside revealed impending cerebral circulatory arrest (Fig. 4B). The patient was diagnosed as brain dead the next day.

6. Case report #5

A 52-year-old man was admitted to the ICU due to coma. He had complained of fever two days previously. No illness was reported in his medical history. On the day of admission to the ICU, he was found unconscious at home with a GCS of 4, and vomiting. He was immediately intubated. After admittance to the ED, the patient tested positive for COVID-19.

A CT head scan revealed a subarachnoid hemorrhage (SAH) caused by a small aneurism of the right ophthalmic artery (Fig. 5A–B). At the same time, given his positive COVID-19 test and the high value of the D-dimer (see Table 1), the patient also underwent a CT thorax scan that revealed a pulmonary embolism (PE), but no lung involvement.

The patient never regained consciousness in the ICU, and developed a severe acute respiratory failure caused by SARS-CoV2 infection. He died after 17 days.

7. Discussion

Intracranial strokes associated with COVID-19 infection have been increasingly reported.[10,11] Despite the increased risk of thrombotic events leading to an expected higher rate of acute ischemic stroke (AIS) among critically ill COVID-19 patients, a non-negligible number of hemorrhagic cerebral manifestations have been highlighted.[12]

COVID-19-associated AIS includes arterial thrombosis due to plaque rupture or embolization. Cases of cerebral vein sinuses thrombosis, which resembles deep vein thrombosis, have also been reported.[13]

Angiotensin converting enzyme 2 (ACE2) receptor, due to its presence in neuronal cells, seems to be an entry point to the brain for SARS-CoV-2, explaining neurological symptoms such as anosmia, dysgeusia and headache.[14,15]

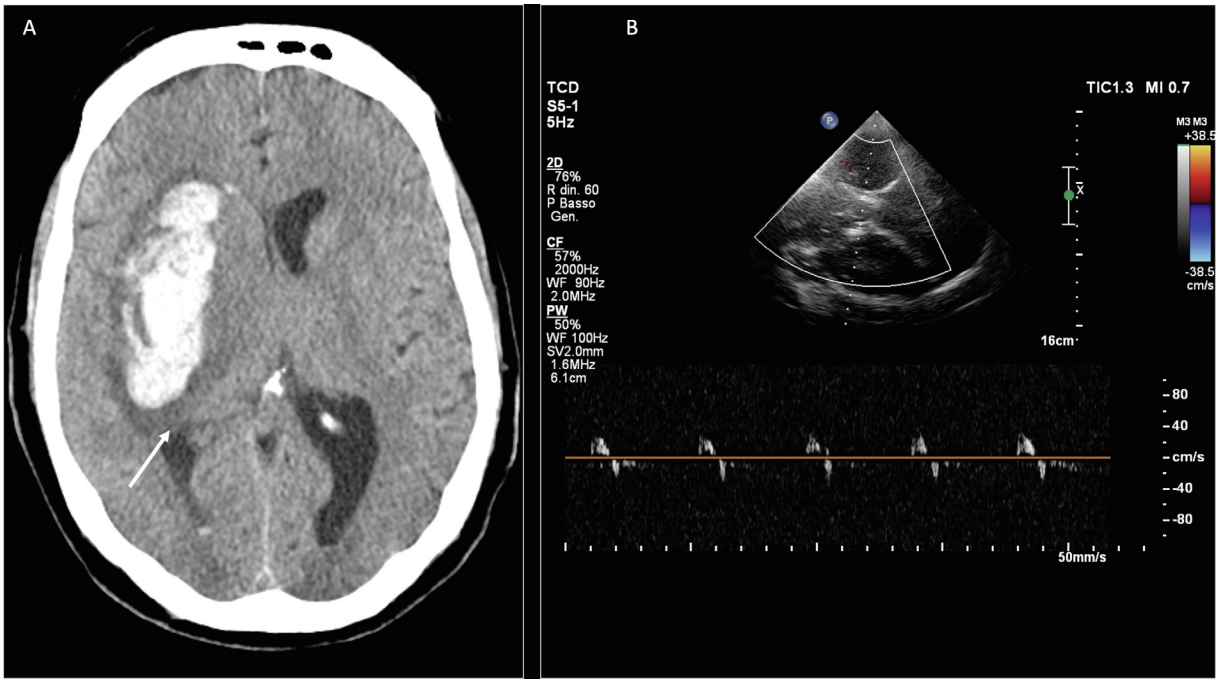

Fig. 4. Axial NECT showing a large inhomogeneously hyperdense right striatocapsular hemorrhage with mass effect on the lateral ventricle (white arrow in panel A). Transcranial doppler evaluation of the right middle cerebral artery demonstrated an impending cerebral circulatory arrest (panel B).

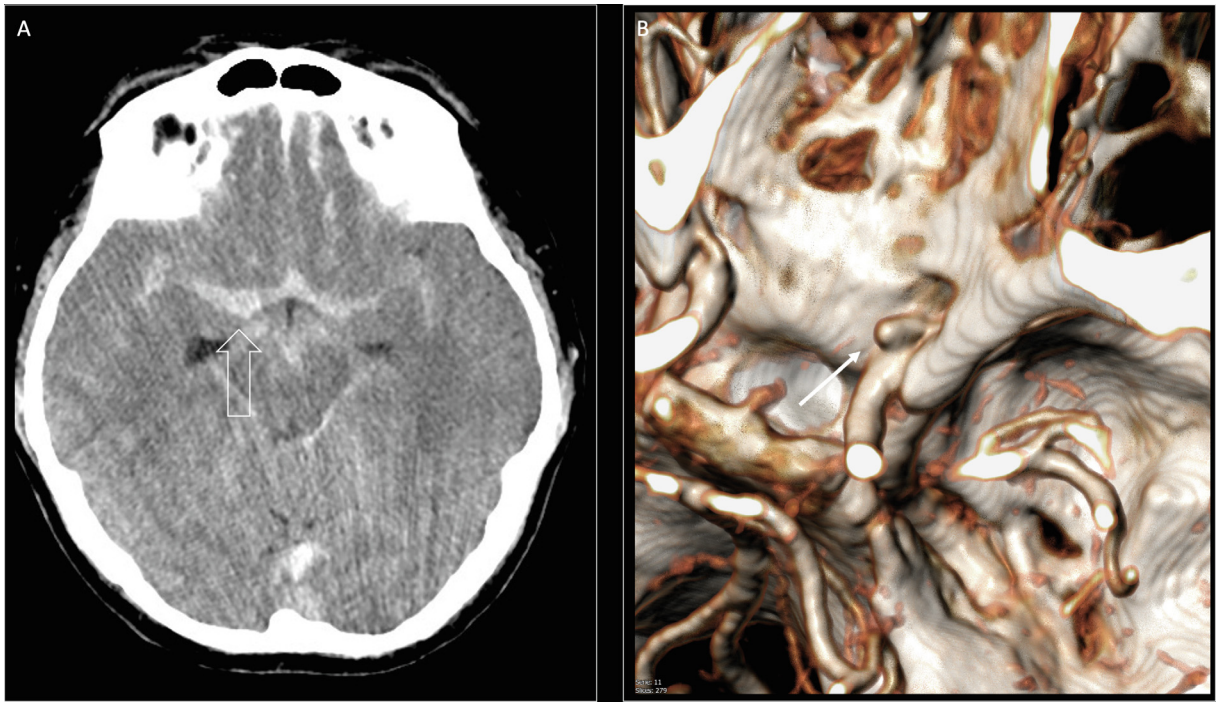

Fig. 5. Axial NECT showing hyperdensity in the basal cistern with slight prevalence on the right side (empty arrow in panel A). The 3D Volume Rendering reconstruction of CTA examination revealed the presence of a small saccular intracranial aneurysm – infundibuloma of the right ophthalmic artery (white arrow in panel B).

However, the etiology of stroke in critically ill COVID-19 patients is probably multifactorial. It seems unlikely that direct cerebral nervous system (CNS) invasion by the virus leads to stroke.[16] The elements of Virchow's triad are blood stasis, endothelial injury and hypercoagulable state, and COVID-19 patients very frequently express all of these.[17] Early on in the pandemic, clinical evidence appeared to support the prothrombotic state of these patients, as well as deep vein thrombosis and pulmonary embolism, especially in the moderate-severe cluster of infected people.[18,19] Based on these findings, and results from autopsies highlighting a high rate of clinically silent PE, international guidelines recommend starting early with pharmacological venous thromboembolism (VTE) prophylaxis.[20–22]

However, the above case reports also included patients who did not experience severe COVID-19 symptoms; rather, they tested positive for SARS-CoV-2 infection with a mild clinical course and no lung involvement.

Evidence supporting an inflammatory state in infected people experiencing mild symptoms could still explain the endothelial injury and hypercoagulable state of the patients in the case reports described.[23]

Moreover, studies have been carried out to investigate the potential impact of immunological responses secondary to an exaggerated response to COVID-19 infection, such as hypoxia, oxidative stress, and excessive platelet-induced aggregation on the brain.[24]

Unfortunately, there have been many delays in the diagnosis pathway throughout the pandemic, and treatment for AIS has been reported in COVID-19 positive patients, leading to increased disability.[25]

Critically ill patients sedated for long periods due to the necessity of mechanical ventilation may likewise make it harder for clinicians to recognize a neurological deficit due to ischemic stroke. For this reason, clinical evaluation should be performed as soon as possible (for instance, periodic lightening of sedation, if possible) in conjunction with multimodal neuromonitoring (TCCD, processed electroencephalogram, near-infrared spectroscopy).[26,27]

Intracranial hemorrhage (ICH) is less frequent than ischemic strokes in COVID-19 patients. However, ICH is associated with a high mortality rate.[28]

At the beginning of the pandemic, an intriguing question was posed by Sharifi-Razavi and colleagues as to whether COVID-19 infection and ICH were coincidental or linked by a causative relationship.[29]

In fact, COVID-19 infection is not an immediate cause of ICH unless the patient is undergoing anticoagulation treatment – a recognized risk factor for ICH in SARS-CoV2 infected patients.[30]

Microscopic studies have demonstrated that viral inclusion is present within the endothelium of the vascular bed, leading to endotheliitis, loss of barrier function, mononuclear infiltration with subsequent disruption of the vascular wall, and finally haemorrhage.[31,32]

It is also possible that hypercytokinemia induces an activation of the matrix metalloproteinases (MMPs) through IL-1, IL-6, TNF-α – a group of proteolytic enzymes that disrupt the vessel walls, which may increase the risk of rupture with consequent bleeding. Finally, a hypercoagulation state may also produce thrombotic microangiopathy of the vasa-vasorum with arterial wall hypoxia, vascular loss of tightness, and rupture.[33]

Patients experiencing ICH have poor outcomes, with the literature reporting a mortality rate in up to 50% of cases.[34]

Reversal of anticoagulation and pressure control are known factors affecting the outcomes of patients with ICH. These measures are hence strongly recommended for these patients.[35] Critically ill COVID-19 patients also develop severe hypoxemia, an aggravating feature for those experiencing ICH.[36]

The literature contains very few SAH case reports of COVID-19 patients, and it remains to be clarified as to whether viral infection may cause SAH.[37–39]

Whether COVID-19 patients suffering from any form of stroke are at increased risk of severe sequelae or death compared to patients testing negative for COVID-19 is a matter of debate.

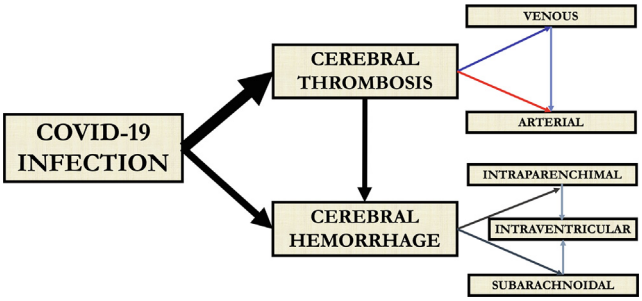

Fig. 6. This figure summarizes the different types of intracranial vascular damage associated with COVID-19 infection.

Compared with non-COVID-19 patients, those with AIS and COVID-19 infection had a higher mortality in a recent large prospective observational study.[40]

These results are in line with the abundance of existing data that uniquely demonstrate that COVID-19-positive patients suffering from AIS have worse outcomes than uninfected patients.[41]

There is less data on ICH than AIS in COVID-19 patients. Articles on this topic predominantly involve case studies. However, the higher mortality rate in COVID-19 patients appears confirmed in this population. Moreover, the literature indicates that ICH is more severe in COVID-19 than non-COVID-19 patients. It affects younger patients, and is probably linked to inflammation rather than hypertension.[28]

Finally, persistent increased risk of stroke in asymptomatic COVID-19 patients suggests that COVID-19 infection in itself – either mild or severe – plays an important role in triggering the sequence of events leading to cerebral vascular damage.[42]

In summary, severe stroke among COVID-19 patients has different features including thrombosis of the arterial or venous cerebral compartment, primary ICH, and hemorrhagic transformation from ischemic lesion (Fig. 6).

Given that COVID-19 is still present worldwide, it should perhaps be included in the differential diagnosis of severe acute stroke patients admitted to the ICU, as well as in COVID-19 patients experiencing mild symptoms with a resolved viral infection and who present with neurological signs.

Ethical approval

The study was approved by the the Regional Ethics Committee (Comitato Etico Unico Regionale of Friuli Venezia Giulia Region). All clinical practices and observations were conducted in accordance with the Declaration of Helsinki.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Patient consent

Informed consent was obtained from patients for publication of this manuscript.

Consent for publication

All the authors have consented for publication of this manuscript.

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