Acute confusional state as a prognostic sign of COVID-19 large-vessel occlusion (LVO)

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SUMMARY

COVID-19 is well known for its respiratory symptoms, but severe presentations can alter haemostasis, causing acute end-organ damage with poor outcomes. Among its various neurological presentations, cerebrovascular events often present as small-vessel strokes. Although uncommon, in predisposed individuals, large-vessel occlusions (LVOs) can occur as a possible consequence of direct viral action (viral burden or antigenic structure) or virus-induced cytokine storm. Subtle presentations and complicated stroke care pathways continue to exist, delaying timely care. We present a unique case of COVID-19 LVO manifesting as an acute confusional state in an elderly man in April 2020. CT angiography revealed 'de novo' occlusions of the left internal carotid artery and proximal right vertebral artery, effectively blocking anterior and posterior circulations. Delirium can lead to inaccurate stroke scale assessments and prolong initiation of COVID-19 stroke care pathways. Future studies are needed to look into the temporal relationship between confusion and neurological manifestations.

BACKGROUND

Coronavirus-2019 disease (COVID-19) is an ongoing pandemic caused by the Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) virus first documented in Wuhan, China, in December 2019. At the writing of this paper, the total number of global cases surpassed 107 million, with over 2 million deaths.[1] SARS-CoV-2 predominantly infects the respiratory system, manifesting as fever, cough, shortness of breath and other systemic symptoms that continue to be elucidated. Simultaneously, the disease has systemic implications, such as acute kidney injury, myocarditis, multiorgan failure and neurological manifestations associated with increased morbidity and mortality.[2 3] Several neurological presentations ranging from encephalopathy to demyelinating syndromes have been implicated, but acute ischaemic stroke (AIS) remains its most devastating manifestation, with the ability to lead to permanent disability.[4] The incidence of AIS in COVID-19-positive patients is 0.7% but increases to 5.7% in patients with severe infection and viral burden.[2 5] Generally, small-vessel pathology comprises most AIS, with large-vessel occlusions (LVOs) constituting 24%–38%.[6]

Epidemiological data on LVOs vary due to discrepancies in its evolving definition. Randomised clinical trials initially included occlusions to the internal carotid artery or M1 of the middle cerebral artery (MCA) that were retrievable by endovascular thrombectomy (EVT). As EVT advanced, the definition expanded to incorporate additional segments of the MCA, anterior cerebral artery, posterior cerebral artery, basilar artery and vertebral artery.[6] Compared with small-vessel strokes, morbidity and mortality significantly increase in proximal LVOs. Advancements in endovascular retrieval systems have considerably improved outcomes in non-COVID-19 strokes. The advent of SARS-CoV-2 has affected several aspects of the LVO definition due to its ability to affect multiple segments from its unique thrombogenic properties. During the 2004 epidemic, 2.43% of SARS-infected patients had LVOs, but the current pandemic incidence has yet to be defined.[7] Here we report a unique case of COVID-19 pneumonia that worsened, eventually developing de novo systemic occlusions of the left internal carotid artery (LICA) and proximal right vertebral artery (RVA), resulting in a massive stroke. We hope to alert clinicians on the ominous findings of delirium in COVID-19-induced strokes, its subsequent effects on mortality and outcomes, and potential recommendations on the fragmented stroke care pathway.

CASE PRESENTATION

A 67-year-old man with a history of multivessel coronary disease, hypertension, peripheral arterial disease, diabetes mellitus type 2, dyslipidaemia and alcohol dependence presented to our emergency department on 17 April 2020 with viral prodromal symptoms, diarrhoea and abdominal cramping for 5 days. He had not taken his routine medications for 3 weeks due to the SARS-CoV-2 outbreak and denied recent travel or exposure to sick contacts. He was on aspirin 81 mg, hydrochlorothiazide 25 mg, amlodipine 5 mg, lisinopril 40 mg, metformin 500 mg two times per day, insulin and ezetimibe 10 mg. On arrival, his vitals read 38.9°C, 116 beats per min, blood pressure of 144/111 mm Hg and respiratory rate of 30 breaths per minute with an oxygen saturation of 98% on room air. Physical exam was unremarkable apart from an ill-appearing man, with initial investigations revealing acute kidney injury and lymphopenia. A chest radiograph revealed patchy infiltrates consistent with pneumonia (figure 1), and he was started on empiric azithromycin, ceftriaxone, hydroxychloroquine with prophylactic enoxaparin. A nasopharyngeal swab sample was sent to the State Department of Health and Human Services, where samples used the real-time PCR under the emergency use authorisation (EUA) by the Food and Drug Administration

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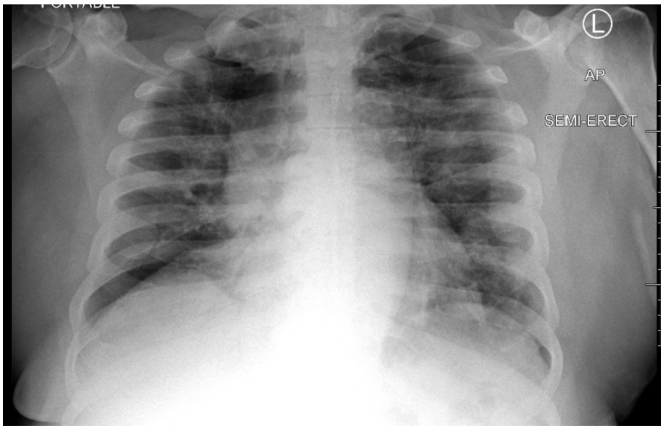

Figure 1 Initial anteroposterior (AP) chest radiograph illustrating bilateral pulmonary infiltrates consistent with COVID-19 pneumonia.

(FDA). Hydroxychloroquine was discontinued shortly after as his glucose-6-phosphate dehydrogenase levels were low and he continued to remain febrile with increasing oxygen requirements necessitating a high-flow nasal cannula. Repeat chest radiography (CXR) revealed multilobar progression (figure 2), prompting a complete COVID-19 inflammatory panel workup that revealed elevated interleukin-6 levels. Lopinavir, ritonavir and tocilizumab were sequentially added to the regimen. His fevers defervesced, and tachycardia improved. Around the early morning of day 7, he was found newly disoriented with rambling and incomprehensible speech. He appeared to struggle in an attempt to remove his gown and was found to have concurrent right-sided facial droop with upper and lower extremity flaccidity. Connected telemetry monitoring revealed sinus tachycardia, most likely from the agitation.

INVESTIGATIONS

A CT head and CT angiography (CTA) was delayed due to acute agitation and decontamination protocols for patients with COVID-19. CT of the head was negative for an acute intracranial bleed, but he was ineligible for tissue plasminogen activator as his last known well time was beyond the allowed 4.5 hours. Aspirin, clopidogrel and atorvastatin were initiated. A request for transfer to nearby tertiary centres for neurointervention was

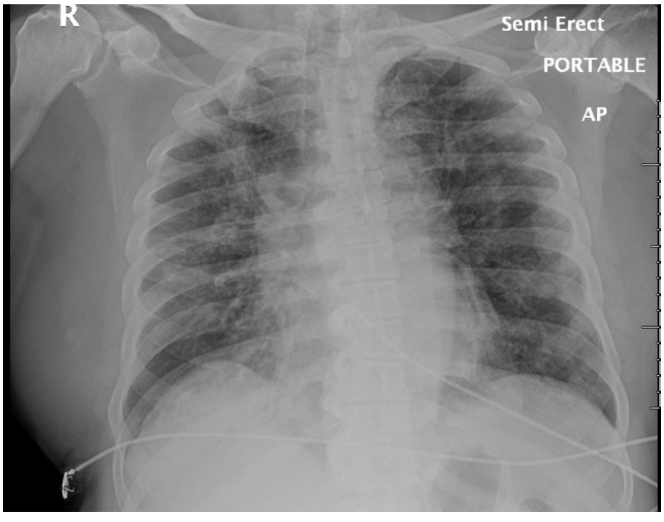

Figure 2 Repeat chest radiograph portraying worsening COVID-19 pneumonia.

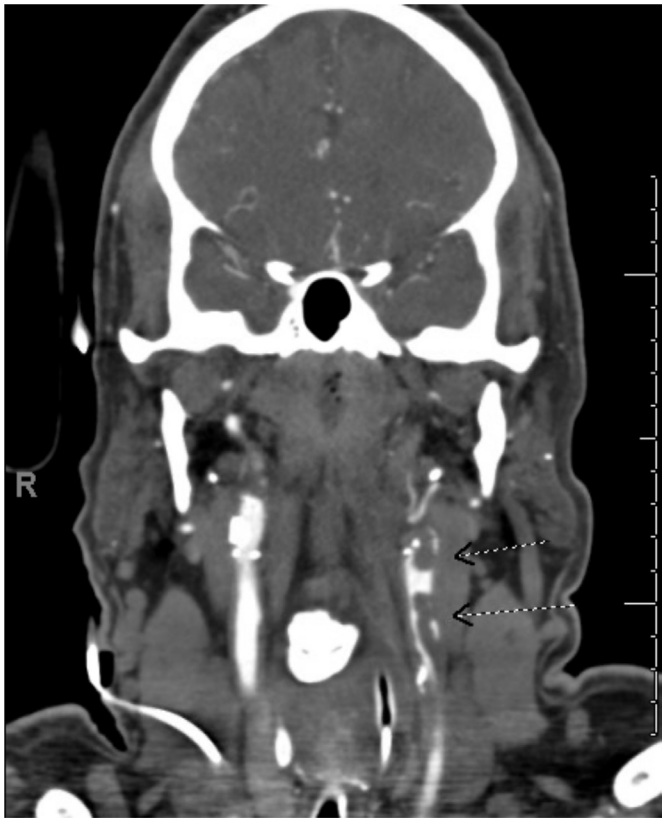

Figure 3 Coronal section computed tomography (CT) with angiography of the head and neck demonstrating complete occlusion at the origin of the left internal carotid artery (arrows).

delayed as centers had enforced strict infection control protocols, making safe transfer with transportation a logistical challenge. Soon after, he developed worsening respiratory failure with increased work of breathing, requiring intubation and transfer to the intensive care unit. A CTA delineated multiple filling defects along the distal portion of the left common carotid artery with complete occlusion at the origin of the LICA (figure 3) and proximal RVA. Additionally, 70%–80% stenosis of the proximal right internal carotid artery (RICA) was noted (figure 4). Electroencephalography (EEG) revealed a focal slowing in the parietal, left and posterior areas of the brain. Ultrasound with Doppler of the lower extremity demonstrated progression of the previously seen right lower extremity deep vein thrombosis (DVT) as well. Two days after that, repeat CT revealed hypodensities within the left frontal and parietal lobes affecting the surrounding insular cortex, suggesting an acute multilobar infarct over distributions of the left anterior and MCA.

DIFFERENTIAL DIAGNOSIS

SARS-CoV2 induced LVO and atherosclerotic mediated LVO were high on the differential, including haemorrhagic stroke, seizures and meningitis. The most likely differential is SARS-CoV2-induced LVO due to SARS-CoV-2 hypercoagulable properties and non-tandem occlusions of the patient's cerebral vasculature including the LICA and proximal RVA. The AIS progressed to a multilobar infarct manifesting as right-sided facial droop with upper and lower extremity flaccidity with associated hyperactive delirium. The patient exhibited underlying vasculopathy with predisposing risk factors. He had a history of hypertension, peripheral vascular disease, diabetes and had an interruption to his medications due to the pandemic, this may

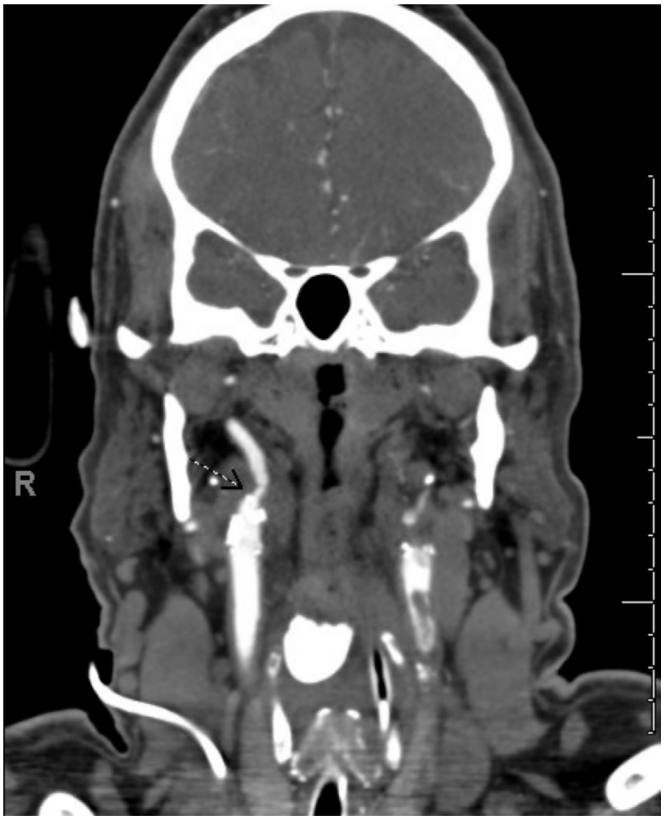

Figure 4 High-grade stenosis of the proximal right internal carotid artery.

have led to flares in his co-morbidities. Our patient did not have a history of atrial fibrillation or hypercoagulability disorder.

OUTCOME AND FOLLOW-UP

His clinical trajectory worsened with higher ventilator requirements, worsening agitation levels and eventual multiorgan failure. Another tertiary centre request was initiated for extracorporeal membrane oxygenation request. Due to his rapidly worsening clinical state and poor prognosis, the family eventually decided to transition to hospice care, where he passed away on 6 May 2020.

DISCUSSION

As COVID-19 continues to spread throughout the globe, our knowledge about the disease process continues to expand. At the time of our patient's presentation, the paucity of information on SARS-CoV-2 and its thrombogenic implications, especially in the setting of time-sensitive strokes, often puzzled clinicians. Simultaneously, critical care pathways, including interfacility transfer that provided timely care, were affected to accommodate the sickest patients with COVID-19. Cerebrovascular disease was seen in 8% of hospitalised patients with COVID-19, even with mild symptoms,[2 8] while its association with AIS has been increasingly identified.[2 9] Although infrequent, SARS-CoV-2-related strokes exceed their counterparts, such as influenza, with an incidence of 0.2%–1.5%, respectively.[10] This finding alludes to the virus's unique thrombogenic features and cumulative disruption of the coagulation and anticoagulation cascades. Specifically, the association between LVO and COVID-19 remains a more rare occurrence. Its spread has been non-uniform, affecting patients below 50 years of age,[11] young men without predisposing conditions[12] and patients with underlying vasculopathy.[13] The distribution of our affected segments in the aforementioned case correlates to the anterior and posterior vascular territories, LICA and proximal RVA, indicating the severity and procoagulant nature of COVID-19. At the same time, the progression of DVT supports the de novo systemic hypercoagulability induced by SARS-CoV-2. At the same time, our patient developed this infarction despite prophylactic enoxaparin; newer studies have recommended therapeutic anticoagulation in severe cases.

Its pathogenesis postulates its propensity to induce hypercoagulability with systemic complications. Multiple mechanisms contribute to the hypercoagulability like hyperviscosity, polyclonal increases in gamma globulins and augmented fibrin breakdown seen by rising d-dimers in the days leading up to stroke. Hypercoagulability in COVID-19 is unique and poorly understood. In contrast, the constellation of the blood–brain barrier and endothelial dysfunction, stasis from prolonged immobility in critically ill patients and the unique ability of COVID-19 to induce hypercoagulability meet Virchow's triad to support this degree of occlusion in our patient.[14 15] An uncontrolled COVID-19 inflammatory response is known as cytokine storm, and in our patient with pre-existing atherosclerosis and plaques, the degree of inflammation from the inflammatory response can rupture the surrounding endothelial cells and contribute to the overall clot burden.[16] Despite thromboprophylaxis, our patient developed a massive clot. In one study, patients with COVID-19 had more thromboembolism episodes than patients without COVID-19 on thromboprophylaxis, eluding to its propensity for clot formation.[17] Neurologically, COVID-19 presents with headaches, dizziness, loss of consciousness, ataxia and seizures.[2] Distinctively, our patient experienced hyperactive delirium and incomprehensible speech a week into hospitalisation. It is important to note that the initial regimen provided to this patient was the only therapeutic choice in our arsenal against COVID-19 due to limited data during the early stages of the pandemic. Since then, several clinical investigations have demonstrated their lack of clinical benefit. At the time of presentation, the use of corticosteroids was not widespread or recommended as the standard of care; with the current knowledge and clinical benefit from dexamethasone in COVID-19, initiation of corticosteroids may have helped quell the infection during the early stages.

This confusional state has been recently recognised in patients with COVID-19.[18 19] Although in-hospital delirium is short-lived, a systematic review found that COVID-19 induced change in mental status to be a marker for increased mortality, length of stay and worse long-term outcomes for patients postdischarge.[20] After completing a literature search, 13 case reports of LVO in SARS-CoV-2-infected patients were identified. Anatomical, laboratory and presenting symptoms are outlined in tables 1–3. Three cases presented with encephalopathic findings: confusion and drowsiness.[21–23] Their outcomes are subsequently listed. Our patient experienced hyperactive delirium features manifested as acute confusion, unorganised thinking and incoherence among these cases. These initial features might signify an impending stroke of moderate to severe degree, although the exact relationship has not been defined. There exists a growing body of literature for encephalopathic findings in SARS-CoV-2-infected patients, but there is no scoring system for prognostication. Further meta-analyses and systematic reviews are warranted to define such measures and to better triage suspected patients. At the same time, cases should be individualised when assessing for cerebral infarctions in patients with delirium. Clinical exam revealing focal deficits can increase pretest probability,

Table 1 Previous COVID-19 large-vessel occlusion strokes

Author and year	Age	Sex	Time to presentation	NIHSS 0 hour	NIHSS 24 hours	NIHSS Follow-up	Outcome status	mRS	Brain imaging NCCT	Brain imaging CTA	Brain imaging MRI	Brain imaging CTP	Vascular territory	R/L
Index case	67	M	7 days	19		Intubated	Died	6	✓	✓			ICA/vertebral	R/L
Mahboob *et al*, 2020[14]	58	F	0 days	15		Intubated	Died	6	✓	✓	✓		PICA	L
Cavalieri *et al*, 2020[21]	33	M		Posterior circulation stroke syndrome			ICU	5	✓	✓			PICA/AICA/SCA	R/L
Roy *et al*, 2020[22]	46	F	3 days	12	18	Intubated	Died	6	✓	✓			ACA/MCA|	R
Popov *et al*, 2020[34]	33	M	14 days				Rehab facility	4	✓				MCA	L
González-Pinto *et al*, 2020[35]	36	F		21			Died	6	✓	✓			ICA/MCA/ACA|	L
Zhao *et al*, 2020[31]	60	M					External transfer				✓			
Duroi *et al*, 2020[36]	74	F	23 days				Died	6	✓				MCA	L
Moshayedi *et al*, 2020[33]	80		5 days				CMO				✓		MCA	L
Co *et al*, 2020[16]	62	F	1 day	4	3	6	ICU	3	✓	✓			MCA	L
Valderrama *et al*, 2020[37]	52	M	7 days	20			Rehab facility	4	✓	✓		✓	ACA/MCA/ICA	L
Guillan *et al*, 2020[23]	67	M	15 days				Rehab facility		✓		✓		MCA/PCA/SCA	R/L
Gunasekaran *et al*, 2020[38]	40	F					CMO	5	✓				MCA	R
Slootjes *et al* 2020[28]	74			16	25	1	ICU	1	✓	✓			ICA	R

ACA, anterior cerebral artery; AICA, anterior inferior cerebellar artery; CMO, comfort measures only; CTA, CT angiography; CTP, CT perfusion; F, female; ICA, internal carotid artery; ICU, intensive care unit; L, left; M, male; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery; R, right; SCA, superior cerebellar artery.

while sicker patients in cytokine storm with sudden changes may warrant a workup.

Our patient also exhibited unique cerebral vasculature findings. CTA revealed a RICA with 80% stenosis from intimal thickening and atherosclerotic calcified plaques, a chronic process that prompted the development of collateral vessels in the left-sided cerebral circulation. For many years, our patient was primarily perfused by his left side. The acute-onset complete occlusion of both LICA and RVA, resulting in a massive stroke, led to our patient's overwhelming deterioration. To our knowledge, only one other case report had simultaneous strokes in both anterior and posterior circulation, making our index case the second.[23] An evidence-based algorithm (SSS Toast) developed for ischaemic stroke aetiology recognition would classify ours under the category 'other', with a probable degree of confidence.[24] Conventionally, LVOs are defined by EVT accessibility with the natural progression of proximal to distal occlusions.[6] In the current SARS-CoV-2 era, LVO incidence has significantly increased from 18.3% in 2019 to 33.8% in 2020.[9] However, there exists no pandemic LVO definition, representing a gap in the literature. Simultaneous occlusions in both anterior and posterior cerebral circulations advocate a possible broadening of the previous LVO concept.

It is well established that stroke pathways quickly screen and diagnose suspected patients for rapid management; here, acute agitation precluded stroke scale assessment, and efforts to expedite imaging were undertaken. COVID-19 disinfection protocols further delayed this expeditious response despite early prompting due to its increasing requirement.[16] Nursing checks were spaced out to limit SARS-CoV-2 exposure. Blood pressure and temperature increase after a stroke.[25] Our patient displayed no change in vital signs on continuous monitoring

Table 2 Laboratory investigations from previous COVID-19 large-vessel occlusion strokes

Author and year	Age	Sex	Pro-inflammatory/Pro-thrombotic biomarkers WBC (k/µL)	Neut$_{abs}$ (k/uL)	Lymph$_{abs}$ (k/µL)	Plt (k/µL)	CRP (mg/dL)	PT (s)	PTT (s)	LDH	D-dimer (ng/mL)	Fibrinogen (mg/dL)	Ferritin (ug/L)	IL-6
Index case	67	M	16.2	↑	↓.	332		15.1	41.6	396	>10		997	62
Mahboob *et al*,[14] 2020	58	F	↔		↓	↔								
Cavalieri *et al*,[21] 2020	33	M				454	2.9			573	3728			
Roy *et al*,[22] 2020	46	F	↑	↑	↓						↑	↑		
Popov *et al*,[34] 2020	33	M				↔		↔	↔		↔	↔		
González-Pinto *et al*,[35] 2020	36	F	23.6				15 600				7540			
Zhao *et al*,[31] 2020	60	M												
Duroi *et al*,[36] 2020	74	F	9.7		↔	↔	18.8	↔			2504	606	846	
Moshayedi *et al*,[33] 2020	80					↔			85.5					
Co *et al*,[16] 2020	62	F	13.2		↓	409	192.0	12.9		406	1160		4609	
Valderrama *et al*,[37] 2020	52	M					1.1				>10 000	235	588	
Guillan *et al*,[23] 2020	67	M	13.1		↔	↔		↔	↔	341	1777	543	1107	
Gunasekaran *et al*,[38] 2020	40	F	14.0	↑		303					28	860	3079	
Slootjes *et al*,[28] 2020	74													

↔, normal; ↓, decreased; ↑, increased; CRP, C reactive protein; F, female; IL, interleukin; LDH, lactate dehydrogenase; Lymph$_{abs}$, absolute lymphocyte count; M, male; Neut$_{abs}$, absolute neutrophil count; Plt, platelet; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell.

Table 3 Previous COVID-19 large-vessel occlusion strokes treatment courses

			Brain Imaging				Vascular territory		Treatment for stroke			Timing of		
Author and year	Age	Sex	NCCT	CTA	MRI	CTP	Vascular territory	R/L	Intravenous tPA	EVT	Other therapy	Intravenous tPA	EVT	Follow-up brain imaging
Index case	67	M	✓	✓			ICA/vertebral|	R/L			Aspirin/clopidogrel/atorvastatin	N/A	N/A	ACA territorial infarcts/MCA territorial infarcts
Mahboob *et al*,[14] 2020	58	F	✓	✓	✓		PICA	L	✓		Aspirin/clopidogrel|		N/A	Focal brain oedema/mass effect|
Cavallieri *et al*,[21] 2020	33	M	✓	✓			PICA/AICA/SCA	R/L			Hemicraniectomy/EVD	N/A	N/A	Obstructive hydrocephalus
Roy *et al*,[22] 2020	46	F	✓	✓			ACA/MCA|	R			Aspirin/hemicraniectomy	N/A	N/A	Diffuse brain oedema mass effect/midline shift
Popov *et al*,[34] 2020	33	M	✓				MCA	L			Intravenous heparin	N/A	N/A	
González-Pinto *et al*,[35]	36	F	✓	✓			ICA/MCA/ACA	L						
Zhao *et al*,[31] 2020	60	M			✓									
Duroi *et al*,[36] 2020	74	F	✓				MCA	L						
Moshayedi *et al*,[33] 2020	80				✓		MCA	L						Haemorrhagic transformation
Co *et al*,[16] 2020	62	F	✓	✓			MCA	L	✓		Aspirin	3 hours 24 min		No ICH
Valderrama *et al*,[37] 2020	52	M	✓	✓		✓	ACA/MCA/ICA	L	✓	✓	Aspirin/atorvastatin			Petechial haemorrhages
Guillan *et al*,[23] 2020	67	M	✓		✓		MCA/PCA/SCA	R/L						
Gunasekaran *et al*,[38] 2020	40	F	✓				MCA	R						
Slootjes *et al*[28] 2020	74		✓	✓			ICA	R	✓	✓		3 hours 0 min	4 hours 30 min	

ACA, anterior cerebral artery; AICA, anterior inferior cerebellar artery; CRP, C reactive protein; CTA, CT angiography; CTP, CT perfusion; EVD, External ventricular drain; EVT, endovascular thrombectomy; F, female; ICA, internal carotid artery; ICH, intracranial haemorrhage; IL, interleukin; L, left; LDH, lactate dehydrogenase; $Lymph_{abs}$, absolute lymphocyte count; M, male; MCA, middle cerebral artery; N/A, not applicable; NCCT, non-contrast CT; $Neut_{abs}$, absolute neutrophil count; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; PT, prothrombin time; PTT, partial thromboplastin time; R, right; SCA, superior cerebellar artery; tPA, tissue plasminogen activator; WBC, white blood cell.

apart from sinus tachycardia from agitation, indicating that haemodynamics are preserved even in patients with massive strokes. In the current pandemic, stroke imaging has decreased by 39%.[26] Studies portray a decreasing mean number of EVTs, and surprisingly, even with interventions, COVID-19-associated clots were refractory and more prone to rethrombosis and reocclusions, suggesting severe ongoing coagulopathy despite clinical defervescence.[9 27] This ultimately fragments the stroke care pathway and results in detrimental outcomes, with a few exceptions.[28 29] The literature recommends establishing a centralised stroke centre with vital clinical research infrastructure as the primary treatment unit.[30] These stroke units can incorporate a framework that can be redeployed towards patient care.[30 31] Reducing inexperienced stroke centres and diverting resources to the centralised unit can lead to prompt EVT by lessening confusion and reducing transit time.[32] Likewise, converting a patient room into an imaging compatible unit and remodelling EVT suites to negative pressure facilities can help mitigate delays and minimise viral transmission.[33] In the face of the COVID-19 pandemic, our care pathways should address these new obstacles so that we can provide high-value stroke care to our patients.

Learning points

- Acute confusional and psychological disturbances in a patient with COVID-19 may be the sentinel presentation of an evolving neurological complication.
- Simultaneous and complete large-vessel occlusion (LVO) in anterior and posterior cerebral vascular territories may be the basis for expanding the current LVO definition, thereby assisting initial triage and management of suspected patients.
- Identification of COVID-19 LVO territories is essential as certain clots are more prone to rethrombosis and reocclusions after mechanical thrombectomy.
- The establishment of an integrated stroke unit and diversion of the severest can lead to prompt treatment in LVO and positive outcomes for patients.
- COVID-19-promoted strokes can be devastating in patients with long-standing cardiovascular disease.

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