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Stroke in patients with COVID-19: Clinical and neuroimaging characteristics

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ABSTRACT

Acute cerebrovascular disease, particularly ischemic stroke, has emerged as a serious complication of infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of the Coronavirus disease-2019 (COVID-19).

Accumulating data on patients with COVID-19-associated stroke have shed light on specificities concerning clinical presentation, neuroimaging findings, and outcome.

Such specificities include a propensity towards large vessel occlusion, multi-territory stroke, and involvement of otherwise uncommonly affected vessels. Conversely, small-vessel brain disease, cerebral venous thrombosis, and intracerebral hemorrhage appear to be less frequent. Atypical neurovascular presentations were also described, ranging from bilateral carotid artery dissection to posterior reversible encephalopathy syndrome (PRES), and vasculitis. Cases presenting with encephalopathy or encephalitis with seizures heralding stroke were particularly challenging. The pathogenesis and optimal management of ischemic stroke associated with COVID-19 still remain uncertain, but emerging evidence suggest that cytokine storm-triggered coagulopathy and endotheliopathy represent possible targetable mechanisms. Some specific management issues in this population include the difficulty in identifying clinical signs of stroke in critically ill patients in the intensive care unit, as well as the need for a protected pathway for brain imaging, intravenous thrombolysis, and mechanical thrombectomy, keeping in mind that “time is brain” also for COVID-19 patients. In this review, we discuss the novel developments and challenges for the diagnosis and treatment of stroke in patients with COVID-19, and delineate the principles for a rational approach toward precision medicine in this emerging field.

1. Introduction

The β-coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), which is responsible for the Coronavirus disease-2019 (COVID-19), has infected 56 million persons and caused more than 1 million deaths worldwide as of 20 November 2020 [1]. While SARS-CoV-2 is known to cause interstitial pneumonia and acute respiratory distress syndrome (ARDS), there is growing evidence of numerous neurological manifestations, including encephalopathy [2], limbic and brainstem encephalitis [3,4], Guillain-Barré syndrome [5,6], and stroke (predominantly ischemic, but also hemorrhagic) [7–11]. These manifestations may reflect either direct viral infection or dysregulation of the immune response which converge in hyper-inflammation processes and, regarding stroke, dysfunction of the coagulation system [12–15]. Stroke in patients with COVID-19 may have distinct characteristics in terms of disease mechanism, patient demographic, but also clinical and neuro-radiological specificities, with implications for diagnosis and treatment.

Herein we discuss the pathophysiology, clinical peculiarities, and main neuro-radiological patterns of stroke in patients with COVID-19.

2. Risk of stroke in COVID-19 patients

Stroke was demonstrated to be an infrequent, albeit potentially life-threatening, complication of COVID-19, affecting approximately 1–3 %...
of hospitalized patients, and up to 6% of those in the intensive care unit (ICU) [12,16–19]. Since male patients are more likely to experience severe SARS-CoV-2 symptoms requiring ICU admission, it is not surprising that the majority of the patients developing stroke during COVID-19 are male (62%), with a median age of 63 years [18]. Importantly, most of the cases present already important vascular risk factors (in particular, hypertension and diabetes mellitus [7,17,18,20]) and, therefore, in this group the infection may simply represent more a trigger than an independent cause. Nevertheless, the importance of COVID-19 as a stroke trigger should not be underestimated, considering that it was observed a 7.6-fold increase in the odds of cerebrovascular complications with SARS-CoV-2 infection as compared to influenza [21]. Typically, patients developed symptoms of COVID-19 infection, including respiratory symptoms and fever, before the onset of stroke, which appeared only 10 days later (delayed presentation) [16,18].

Race/ethnicity is an important risk factor for severe COVID-19 infection, and this is likely due to an over-representation of cardiovascular risk factors in some specific ethnic groups (e.g. Black patients had the highest prevalence of obesity, hypertension, and diabetes in a study involving 7868 cases hospitalized with COVID-19 [22]) and possibly to longstanding racial/ethnic health and socioeconomic inequities. The consequence of these factors is the uneven distribution of the different ethnic groups among patients with COVID-19-related stroke: in a recent study involving 83 cases, 47% were Black, 28% Hispanic, and 16% White [23].

Young-onset cases of stroke (<50 years) were also observed [10], and this group seems to have distinctive clinical characteristics: (1) previous risk factors and comorbidities appear to be rare/absent, (2) stroke tend to occur before the onset of COVID-19 symptoms, (3) large-vessel occlusion seems frequent, and (4) it is postulated that in this cohort of otherwise healthy individuals COVID-19 plays a major role to cause stroke [10,20,24].

3. Clinical presentation

Patients with COVID-19 appeared to be particularly prone to (1) large vessel occlusion (including occlusion of the internal carotid artery, M1 and M2 segments of the middle cerebral artery [MCA], and the basilar artery); (2) multi-territory involvement; (3) involvement of otherwise uncommonly affected vessels [7,9,11,19,25], including for example the occlusion of the pericallosal artery [7], or the presence of multiple focal stenoses in the V4 segment of the vertebral artery [11]. The resulting neurological deficit was typically severe (reported median National Institutes of Health Stroke Scale, NIHSS, ranging from 19 to 21), and about one quarter of the cases had evidence of systemic thrombosis, including venous thrombosis, pulmonary, and spleen embolism [7,18,25]. Overall, more than 40% of the patients were diagnosed with cryptogenic stroke, often with an embolic radiologic appearance. Conversely, small vessel pattern was infrequently reported [18,19].

Laboratory features included coagulopathy (elevated fibrinogen, elevated D-dimer), high incidence of hepatic and renal dysfunction, and elevated lactate dehydrogenase (LDH) [7,9]. Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein antibodies) were detected in a significant proportion of cases [13,18]. Bleeding manifestations were not frequently observed, differentiating SARS-CoV-2 coagulopathy from that seen in infections by other RNA viruses such as Ebola and other hemorrhagic fever viruses [13].

The distinctive characteristics of stroke in patients with COVID-19 (summarized in Table 1) require an ad hoc approach to diagnosis and management. The need of a “protected code stroke” [26] is emphasized in Fig. 1, as well as the need to quickly identify patients with infection (through nasopharyngeal swab) and those with concurrent pneumonia (pulmonary imaging using chest computed tomography [CT] may be incorporated in the initial imaging for stroke) [27]. Given the relatively high incidence of acute kidney injury related to COVID-19, particular

Table 1

| Incidence and demographic features | - 1 to 3% of hospitalized COVID-19 patients, 6% of those critically ill |
| Proposed pathogenesis | - Cytokine storm–triggered hypercoagulable state |
| Typical features | - Large vessel occlusion |
| Less typical presentations | - Bilateral carotid artery dissection |
| Laboratory features | - Positive lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein have been reported |
| Predictors of outcome | - Older age, higher baseline NIHSS, elevated D-dimer, glucose, and creatinine concentrations were associated with poor outcome |
| Management issues | - Need for a “protected code stroke” |

Abbreviations: ARDS, acute respiratory distress syndrome, COVID-19, coronavirus disease 2019, ICU, intensive care unit, LDH lactate dehydrogenase, NIHSS; National Institutes of Health Stroke Scale; PRES posterior reversible encephalopathy syndrome, SAH, subarachnoid hemorrhage.

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4. Neuroimaging features

Acute ischemic stroke represents the most common neuro-radiologic abnormality seen among COVID-19 patients with neurological manifestations, usually (60–65 % of the cases) involving the large vessels [10, 19,28]. Multiple vascular territory infarction was frequent, affecting 27/103 (26 %) of the cases, while small vessel occlusion was reported in only 9/103 (9 %) of cases [18]. Acute ischemic stroke in the vertebro-basilar territory was also common, being observed in 6/17 (35 %) of patients [11]. Frequent occurrence of posterior circulation stroke has been also confirmed by other authors [8,9].

The role of hypercoagulable state is strongly suggested by report of patients with high D-dimer values, CTA confirmed occlusion of anterior cerebral artery (ACA) or MCA and co-occurrence of floating thrombi in the ascending aorta [29], common carotid artery and/or internal carotid artery [10,30]. Cavallieri et al. discussed the case of a young man with increased D-dimer and fibrinogen, elevated LDH and mild thrombocytosis who developed bilateral cerebellar ischemic lesions due to CTA confirmed occlusion of the left vertebral artery, posterior inferior cerebellar artery (PICA) and bilateral anterior inferior cerebellar artery (AICA) [31].

Vasculitis or vasculitis-like phenotype (including pediatric focal cerebrovascular disease) has been reported in two pediatric and three adult patients with acute ischemic stroke [32–36]. Interestingly, two of these cases showed arterial wall enhancement on magnetic resonance (MRI) imaging consistent with inflammation. In the adult patient the vasculitic process was extensive, involving the ACA bilaterally, MCA, vertebral arteries, and basilar artery [35]. Several viral pathogens such VZV, herpesviruses, HIV, and influenza A have been associated with arteriopathy. In particular, VZV vasculopathy is often characterized by multiple vascular territory ischemic strokes [7,37,38].

Information concerning intracerebral hemorrhage (ICH) in COVID-
19 patients is still limited but available data suggest that hemorrhagic events occur in 0.5%–0.9% of patients [19]. Hemorrhagic stroke has been reported from 21.7% (5/23) [11] to 25.7% (9/35) [39] of SARS-CoV-2 infected patients with stroke. Hemorrhage may be massive with extensive hemispheric involvement [39,40], and/or with multiple hematomas occurring in both supra and infra-tentorial locations [7,41,42]. Parenchymal hemorrhages may occur spontaneously in critically ill patients, particularly in the context of multi-organ failure (MOF) and circulation instability [7,42], or as complication of other pathologic conditions, such hemorrhagic transformation of acute ischemic stroke [43], rupture of pseudo-aneurism [44], or hemorrhagic infarction associated with cerebral venous sinus thrombosis (CVT) [45]. CVT is apparently not frequent in COVID-19, with only 18 patients reported [19,46,47]. Malentacchi et al. described concomitant arterial and venous thrombosis in one elderly patient with ischemic lesions due to CTA-demonstrated bilateral occlusion of MCA and a filling defect in the right sigmoid sinus consistent with thrombosis [48].

Interestingly, some case reports suggest a potential correlation between COVID-19 and arterial dissection involving extra-cranial vertebral artery [11,49] or carotid artery [50], including patients with unremarkable medical history or cardio-vascular risk factors. In one case [51], cervical vertebral artery dissection was associated with digital subtraction angiography-confirmed reversible cerebral vasoconstriction syndrome (RCVS) involving the anterior circulation associated with bilateral frontal subarachnoid hemorrhage (SAH). Al Saiegh et al. described a case of massive SAH in the posterior fossa and in the fourth ventricle due to rupture of a dissecting aneurysm of the PICA [43].

It is possible that SARS-CoV-2 engagement of angiotensin-converting enzyme 2 (ACE2) on the surface of endothelial and arterial smooth muscle cells allows the virus to damage cerebral arteries causing arterial wall dissection or rupture with hemorrhage. Furthermore, as previously described, dysregulation of the renin-angiotensin system causes enhanced availability of angiotensin II which induces vasoconstriction and immunological activation, a process leading to loss of self-regulation, alteration of blood-brain barrier, cerebral hypoperfusion and vasogenic edema [52]. These mechanisms provide a conceptual framework for interpretation of the neuro-radiological findings described in the literature. Fig. 2 shows some examples of neuroimaging findings in patients with stroke developing during SARS-CoV-2 infection.

5. Atypical neuroimaging features

Helms et al. reported brain perfusion abnormalities in 11 out of 11 COVID-19 patients with ARDS who underwent MRI with perfusion weighted imaging [53]. The same authors also noted that most patients who underwent MRI for encephalopathy showed leptomeningeal enhancement (8 cases), two of them with asymptomatic focal acute ischemic stroke and one with a subacute ischemic lesion. Similar findings were also described in one patient with encephalopathy discussed by Morassi et al. where two small ischemic lesions co-existed with focal cortico-pial enhancement [7]. Cases of posterior reversible encephalopathy syndrome (PRES) in severe SARS-CoV-2 infection have been also described [46], the majority characterized by diffusion restriction and hemorrhagic lesions including macrohemorrhages, microbleeds, and SAH [11,54]. Leuko-encephalopathy with various types of non-specific T2-FLAIR hyperintense lesions and numerous microhemorrhages have been reported in critically ill COVID-19 patients studied with MRI [55–57] and considered to be hypoxia-related. Anzalone et al. presented four cases of severely ill COVID-19 patients with cortical laminar lesions

Fig. 2. Neuroimaging features of COVID-19-associated stroke.
A-B: A 80-year-old man with COVID-19 and critical ARDS developed acute left-sided weakness. Brain CT-angiography showed a distal complete occlusion of the right middle cerebral artery (A). Brain CT demonstrated a large fronto-insulo-temporal ischemic lesion within the vascular territory of the right middle cerebral artery (B).
C-D: A 75-year-old man with COVID-19 and critical ARDS abruptly developed severe hypoxemia due to suspected pulmonary thromboembolism and left-sided hemiparesis. Brain CT showed infarctions in multiple vascular territories, including one lesion in the right parietal region (C) and in the left cerebellar hemisphere (D). E-F: A 68-year-old man with severe COVID-19 presented delirium followed by dysarthria and left lower limb paresis. MRI showed two punctiform ischemic lesions characterized by diffusion restriction on DWI in the left superior frontal gyrus (E) and in the pons (F).
Abbreviations: ARDS, acute respiratory distress syndrome, COVID-19, coronavirus disease 2019, CT, computed tomography, DWI, diffusion weighted imaging; MRI, magnetic resonance imaging.
with PRES-like predominantly parieto-occipital distribution, showing diffusion restriction in two cases [58]. The normalization of MRI picture in one patient suggests that these findings may be the result of potentially reversible alterations of the cerebral microcirculatory function. Alteration of the blood–brain barrier permeability may disrupt the local homeostasis of extracellular contents resulting in cortical dysfunction and ischemia [58].

In conclusion, this constellation of neuroimaging findings clearly indicates that underlying thrombotic angiopathy, direct vascular damage, and dysfunction of the vascular autoregulation of the brain may coexist in COVID-19 patients with neurological manifestations. Awareness of these pathophysiologic mechanisms and the recognition of their neuroimaging counterpart is of utmost importance for a timely diagnosis and management.

6. Outcome

The functional prognosis was unfavorable in more than 70 % of the cases in a recent study [11], and high mortality was also detected by other groups [7,18]. Importantly, the outcome of COVID-19-related stroke cases was significantly worse than that of non-COVID stroke cases in 2 different studies performed in Italy and USA, respectively [59,60]. The mortality rate was particularly high in cases with stroke ensuing in association with severe respiratory disease requiring ICU admission [7]. In general, the development of major neurological manifestations (defined as the presence of encephalopathy, stroke, or seizures) during the course of SARS-CoV-2 infection was found to be an independent predictor of death in hospitalized patients [61]. For cerebrovascular disease, some of the predictors of poor outcome were in line with the experience in non-COVID stroke cases, such as older age, higher NIHSS at admission, baseline glucose, and creatinine levels, while others appear to be more specific to this particular population (e.g. thrombocytopenia, lymphocytopenia, and elevated levels of D-dimer and LDH) [7,11,13,19,60,62].

7. Stroke mechanisms in COVID-19

The pathogenesis of stroke during infection by SARS-CoV-2 is complex and not fully understood, but current evidence points towards the combined effect of (1) virus-related factors; (2) characteristics of the host; (3) virus-host interactions.

SARS-CoV-2 enters cells by binding of its spike protein to ACE2 [14,63]. Following the binding of the virus, there is an important decrease of expression and activity of ACE2 due to cleavage and shedding of its extracellular component. The downregulation of ACE2 expression reduces its protective effects and exacerbates the injurious actions (prothrombotic and proinflammatory) of angiotensin II [14,62,63]. The host responds to the aggression of SARS-CoV-2 by stimulation of immune cells (the role of macrophages seems particularly relevant) which lead to the delivery of cytokines, comprising IL-6 and IL-1β [15]. A previous study performed in patients with ARDS found that increased IL-6 levels correlated with increased fibrinogen concentrations, establishing a link between inflammation and prothrombotic changes [64]. An alternative vasculitis-like mechanism, similar to that of varicella zoster virus (VZV), seems also plausible [16]. To this regard, viral replication in endothelial cells causes apoptosis and local inflammation has been shown in kidney, heart, and lung [65], suggesting that the latter may apply also for the brain. In a recent report which also analyzed brain biopsies from patients with COVID-19 and stroke, signs of thrombotic microangiopathy and endothelial injury were found [11]. Indeed, the combination of thrombocytopenia, elevated D-dimer, and C-reactive protein observed in severe COVID-19 are consistent with a virus-related microangiopathic disorder [16]. Inflammatory cytokines may also promote activation of matrix metalloproteinases and degradation of extra-cellular matrix, providing the conditions for a weaken vessel wall and arterial dissection [50].

Characteristics of the host, both pre-existing (known vascular risk factors) and specific of the infection phase (dehydration due to fever, protracted immobilization, and acute cardiac injury) appear to be also crucial. In particular, cardiac involvement was shown to be present in 78 % of German patients recently recovered from COVID-19 studied using cardiovascular MRI, while 60 % demonstrated ongoing myocardial inflammation [66]. In agreement with these findings, clinically significant arrhythmias have been reported in approximately 10 % of hospitalized patients with COVID-19, and up to 40 % in those critically ill [12,28,67,68].

8. Final comments

As clinical evidence accumulates, it appears that stroke in the context of COVID-19 infection may have distinct pathogenetic mechanisms and clinical characteristics. Moreover, some management issues specific to this population have emerged, including the need for a protected pathway for brain imaging, intravenous thrombolysis, and mechanical thrombectomy, as well as the difficulties in identifying clinical signs of stroke in critically ill patients in the intensive care unit. A precision-medicine approach that takes into account these clinical, diagnostic, and therapeutic specificities is therefore advisable.

Authors’ contributions

Study concept and design: AV, MM
Drafting of the manuscript: AV, MM
Critical revision of the manuscript for important intellectual content: AV, GLG, CB, MM
Study supervision: AV, MM
All authors read and approved the final manuscript.

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Data access, responsibility, and analysis

The Corresponding Author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Competing Interest

None reported.

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