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COVID-19 IMPLICATION AS RISK FACTOR FOR STROKE

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Abstract

COVID-19 has become a global pandemic, affecting millions of people. This aerosol infection caused by SARS-CoV-2 possesses a wide range of symptoms; from being asymptomatic to fatal symptoms, from simple (cold, cough and flu) to severe pneumonia and respiratory distress. But, COVID-19 can affect other organs, including the brain (central and peripheral nervous system). COVID-19 patients presented a wide range of neurological symptoms (headache, dizziness, anosmia, ageusia, confusion) and neurological disorders (encephalitis, encephalopathies, myelitis, cranial nerves damage, Gullian-Barre polyradiculoneuritis and its variants, neuropathies, myopathy, seizures, neurodegenerative diseases), among which stroke is the most prevalent and devastating, presented as an independent risk factor for poor prognosis.

Several studies of acute stroke in COVID-19 patients reported both acute ischemic stroke and acute cerebral hemorrhage (up to 6% of individuals with COVID-19 suffered acute stroke).

The stroke risk was highest in those most severely infected and those with pre-existing vascular risk factors. Most strokes were ischemic and there was an increase in the large vessel occlusion, suggesting that cerebral thrombosis and/or thromboembolism could be possible causative pathways for the disease.

The relationship between COVID-19 and acute stroke is unclear. The pattern of stroke differs from that in a non-COVID-19 stroke population. The understanding of the underlying mechanism between COVID-19 and stroke warrants further study, so does the development of an effective therapeutic or preventive intervention.

***Keywords*:** COVID-19, SARS-CoV-2, stroke, ischemic stroke, hemorrhagic stroke

Introduction

Coronavirus disease 2019 (COVID-19) pandemic has become a global pandemic, affecting millions of people, leading to unprecedented challenges. COVID-19 is not just a respiratory disease. This aerosol infection has done multi-organ and systems failures. Like most of the medical disciplines, neurology has been impacted by COVID-19 pandemic as well. A vast amount of scientific data report that the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which currently prevails all over the world, also infects the brain (the central and the peripheral nervous system) causing neurological disorders [1].

The common symptoms of COVID-19 include fever, dry cough and shortness of breath [2], but neurological features are also recognized as common manifestations of the COVID-19, especially in the cases of severe infection [3].

Central nervous system is affected with encephalitis [4,5] acute necrotizing hemorrhagic encephalitis, encephalopathy, seizure [6], myelitis [7] and the most frequent, stroke (ischemic type) [3] and **peripheral nervous system** with Guillain-Barre syndrome and its variants**,** anosmia 5-98% [3], ageusia 45-88%, myopathy and neuropathy.

Stroke represents more than a quarter of the neurological manifestations associated with COVID-19. These are most ischemic types of strokes. Often extensive, these strokes affect patients with additional vascular risk factors such as high blood pressure, obesity, diabetes, atrial fibrillation, congestive heart failure or other risk factors (kidney disorders). Despite the presence of these factors, the exact cause of these strokes remains unidentified in two-thirds of cases of COVID-19 [8].

During this infection, hypercoagulability, the result of the hyperinflammatory state and infection of the vessel wall by the virus itself have been reported [9]. The association of ischemic stroke

and SARS-CoV-2 infection is not trivial, since hospital mortality is particularly high (≈ 16%). Recent studies in Wuhan have shown that 5% of patients admitted for COVID-19 infection presented with ischemic stroke which increased the risk of mortality by 38% [10].

Neurotropism of COVID-19

Coronaviruses (CoVs) are a group of enveloped viruses with a single stranded, positive sense ribonucleic acid genome [11]. Based on the phylogenetic characteristics, they are divided into four groups: alpha, beta, gamma and delta-CoVs [12].

The spike (S) protein appears to be the key structure for infectivity and virulence as it recognizes and binds to the receptors on the host cells [12,13].

The envelope of the beta-CoVs consists of five structural proteins, known as spike. Respiratory droplets and contact are the main routes of transmission for COVID-19; however, there is also evidence for transmission through the digestive tract or through aerosols during a prolonged exposure [12].

The neurotropism of CoVs is known, particularly the neurotropism of the beta-coronavirus family. One of the preferred pathways for entry of the virus into the brain would be retrograde neuronal dissemination via the olfactory mucosa, and then the olfactory bulb [2].

The hematogenous direct route or via myeloid cells is also possible [14]. The paths are not precisely known, but it seems that viruses use synaptic pathways to pass from the cardiorespiratory center to the spinal cord. The mechanoreceptors and chemoreceptors of peripheral nerve endings that are found in the lower respiratory tract are believed to be the gateway through which the virus reaches the central nervous system.

Neurological symptoms, signs and disorders due to COVID-19

The neurological symptoms of COVID-19 affect only a minority of people: 8% suffer from headaches and 1% from nausea and vomiting. In contrast, a study with COVID-19 patients described neurological manifestations such as loss of consciousness and acute stroke in 88% of the severe cases [3].

Anosmia and ageusia have been very commonly seen as minor neurological manifestations.

But, Guillain-Barre syndrome (polyradiculoneuritis), acute disseminated encephalomyelitis, acute necrotizing hemorrhagic encephalitis and myelitis have been reported as major neurological disorders due to COVID-19. Patients with severe forms of COVID-19 and acute respiratory syndrome suffered from neurological damage, mainly encephalopathy, confusion and corticospinal signs [2].

Risk factors for stroke in COVID-19 patients

Stroke risk is high in people with risk factors like high blood pressure, obesity, diabetes, high cholesterol, atrial fibrillation and smoking, but with COVID-19 there is an increased prevalence of stroke [15].

The studies reported that acute stroke incidence in COVID-19 patients was approximately 0.9%-2.7%. COVID-19 patients that developed acute stroke were older than infected patients without stroke (median age 65.3 years); majority of them were Black people and had preexisting comorbidities (atrial fibrillation, congestive heart failure, obesity, chronic kidney disease, severe infection-pneumonia) and the largest number were males (62.4%). Stroke risk in COVID-19 was higher in patients with cardiovascular risk factors: hypertension (62.2%), diabetes mellitus (36.7%), dyslipidemia (25.2%) and coronary artery disease.

There was no significant difference in rates of smokers *versus* non-smokers. In two Chinese retrospective series, approximately 6% of COVID-19 patients developed stroke (cerebral venous thrombosis or cerebral hemorrhage) within 10 days of the first symptoms; these patients were older; had more cardiovascular comorbidities and more severe pneumonia [3].

Some other studies found that COVID-19 symptoms were presented at acute stroke onset in 84.1%; the median delay of stroke from COVID-19 symptoms onset was a few days (8.8 days). When analyzing the clinical reason for admission (COVID-19 symptoms *vs*. stroke symptoms), it was found that neurological symptoms related to stroke represented the reason for hospital admission in 37.7% of patients.

In general, laboratory investigations showed elevated median D-dimer (3720 mg/L) and fibrinogen (459 mg/L) levels. Interleukin-6, C-reactive protein and platelet were also increased in COVID-19 patients [16].

Data on antiphospholipid antibodies were as follows: 17.2% were positive for immunoglobulin M/G, anticardiolipin or anti-b2-glycoprotein I antibodies [17].

This could be attributed to the hypercoagulable state that predisposes COVID-19 patients to thromboembolic incidents.

As a prognostic factor Prananta *et al*. [18] reported that stroke was associated with mortality in COVID-19 patients or COVID-19 patients with stroke have poor outcomes. The in-hospital mortality and discharge to destination other than home were significantly higher in patients with COVID-19 and acute ischemic stroke compared to those without stroke.

Pathophysiological mechanism between COVID-19 and stroke

The mechanisms of stroke in people with COVID-19 are likely multifactorial. They could be related to conventional stroke mechanisms, with COVID-19 acting as a trigger [19, 20]. Alternatively, they could be directly caused by SARS-CoV-2 infection through specific pathophysiological mechanisms, leading to both ischemic and hemorrhagic stroke.

Ischemic stroke mechanism in COVID-19

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE-2) receptor with viral surface S proteins and gains entry to host cells [21]. ACE-2 is widely expressed in human body, specifically the neurons, glial cells, endothelial cells and arterial smooth muscles in the central nervous system [21]. This renders them vulnerable targets to SARS-CoV-2. Although the exact neurotropism of SARS-CoV-2 is still disputable, the affinity of SARS-CoV-2 S protein to ACE-2 receptor is 10 to 20-fold higher than that found in SARS-CoV-1 [22].

The cause of stroke, however, is plausibly multifactorial. Coagulopathy and hypercoagulability as a result of systemic response to SARS-CoV-2 infection, endothelial injury caused by direct viral invasion, and venous stasis due to immobilization, are all implicated in stroke in COVID-19 patients. Hyperviscosity is another risk factor for thrombosis. In addition to direct impairment of organ function, a cytokine storm contributes to hyperviscosity as well. In return, hyperviscosity impairs endothelium and promote hypercoagulable state.

The pattern of stroke in COVID-19 differs from that in non-COVID-19 stroke patients. Ischemic stroke in COVID-19 patients was frequently characterized by multiple cerebral infarctions and cryptogenic etiology. The most common stroke mechanism in acute ischemic stroke was cryptogenic in 44.7%, followed by cardioembolism (21.9%), large vessel atherosclerosis (occlusion pattern) in 79.6% and multiple territory infarcts in 42.5%, suggested increased thrombosis and thromboembolism. Small artery stroke was infrequently reported (3.3%).

In a systemic review conducted in 2020, Ghannam *et al*. [23] reported that 48.8% of neurological involvement in COVID-19 patients were stroke incidents, which consisted of 87.5% ischemic stroke (5% cerebral venous thrombosis), 5% intraparenchymal hemorrhage, and 2.5% subarachnoid hemorrhage. The majority of ischemic stroke subtype was large vessel occlusion, which consisted of 77%. However, in a retrospective cohort study examining COVID-19 and stroke, Yaghi *et al*. [17] reported that large vessel disease consisted of only 6.2% and the majority of stroke subtypes was cryptogenic.

Hemorrhagic stroke mechanisms in COVID-19

COVID-19-related hemorrhagic strokes are much less common than ischemic strokes. Whether the COVID-19 infection and intracerebral hemorrhage are casually related, it is unclear. However, some mechanisms mediating the increased risk of ischemic stroke in patients with COVID-19 could also play a role in promoting intracranial bleeding [24].

The affinity of the SARS-CoV-2 for ACE-2 receptors could allow the virus to directly damage intracranial arteries, causing vessel wall rupture.

Also, downregulation of renin-angiotensin system may rise blood pressure and put patients already diagnosed with hypertension at higher risk of hemorrhagic stroke [25].

Older individuals, affected by age-related ACE-2 deficiency, might be particularly exposed to risk of intracerebral hemorrhage.

The integrity of blood brain barrier could be impaired by the massive release of cytokines and proteases that accompanies the immune response to the SARS-CoV-2 infection [25, 26].

Besides the intracerebral hemorrhage, blood brain barrier breakdown could explain the cases of hemorrhagic posterior reversible encephalopathy syndrome and hemorrhagic transformation of ischemic strokes [26].

Also, SARS-CoV-2 infection could be associated with a consumption coagulopathy related to fibrinogen depletion (either from metabolic acidosis or disseminated intravascular coagulation) which may increase the risk of intracerebral hemorrhage. Patients with intracerebral hemorrhage showed a strictly lobar hematoma in 44.1%, and the volume of hematoma led to intracranial herniation in 18.5%.

Direct neural invasion via ACE-2 receptors and dysregulation of blood pressure have been postulated as potential underlying mechanisms for hemorrhagic stroke [27].

Future studies are needed to identify the risk factors, mechanism and outcomes of hemorrhagic stroke in patients with COVID-19.

The role of COVID-19 in the occurrence of stroke in younger patients

The rate of stroke in COVID-19 is reported with an increased incidence in younger patients, and the strokes are often more serious compared to those occurring in people not infected with SARS-CoV-2 [3].

Yaghi *et al*. [17] found that COVID-19 patients with stroke were generally younger and with higher National Institutes of Health Stroke Scale score on admission than their counterparts without COVID-19. This could be attributed to the hypercoagulable state that predisposes COVID-19 patients to thromboembolic incidents.

During the height of the pandemic in New York City, some COVID-19 young patients with no vascular risk factors were hospitalized because of large vessel stroke [28].

This was a 7-fold increase in the rate of large vessel stroke in young people compared to the previous year and the patients had laboratory findings that suggested a hypercoagulable state, leading to the postulation that stroke was probably related to the presence of SARS-CoV-2 in these young patients [29].

In patients presenting with large vessel stroke during the pandemic, data from the Mount Sinai Health System in New York City confirmed that patients who tested positive for SARS-CoV-2 were significantly younger, with a mean age of 59 years compared to patients negative for SARS-CoV-2 who had a mean age of 74 years [30].

Patients with COVID-19 who had imaging confirmed stroke and were admitted to another large New York City medical centre were again found to be younger, with a mean age of 63 years, than a control group of patients with stroke who tested negative for SARS-CoV-2 and had a mean age of 70 years [17].

A case-control analysis of acute stroke protocol imaging (New York City Health System) showed that, after adjusting for age, sex, and vascular risk factors, SAS-CoV-2 positivity was independently associated with stroke in younger individuals.

In several thrombectomy case series of COVID-19 patients were younger than the typical population having this procedure.

A multicentre series of patients with COVID-19 (ischemic or hemorrhagic events) reported that 27% were younger than 50 years [31]. Some of them with large vessel stroke, without previous stroke risk factors and far worse in terms of clinical outcomes than patients with stroke who did not have COVID-19 (this is probably related, in part, to the COVID-19 disease process).

The death rate among young patients with COVID-19 and stroke is reported to be high (55%). Most of them are reported secondary to hypercoagulability. Patients in their 30s to 40s and who did not necessarily have severe forms of the COVID-19 have died of stroke [15].

In conclusion, some mechanisms directly related to COVID-19 have a role in the occurrence of stroke and explain the characteristic profile of stroke in infected patients. Large artery occlusion in COVID-19 may be primarily due to cardioembolism (or paradoxical embolism) and less often due to large artery atherosclerosis and plaque rupture [32].

This explains the occurrence of stroke among young people without vascular risk factors, in individuals with high levels of D-dimer or other signs of hypercoagulability or in patients with pulmonary embolism and venous thrombosis [33].

The understanding of the mechanism between COVID-19 and stroke warrants further study, so does the development of an effective therapeutic or preventive intervention. While traditional stroke treatments are still being given to patients having both stroke and COVID-19, it is still unclear what the best treatments are.

For now, the recommendations of experts will be of help to those involved in healthcare to develop treatment strategies and adopting of specific safely care protocols for COVID-19 patients with stroke (a guidance for care of stroke patients during COVID-19 pandemic is released by the American Heart Association and the American Stroke Association).

Conclusion

COVID-19 pandemic has an impact on every aspect of healthcare and neurology is no exception. Acute strokes are not uncommon in patients with COVID-19, especially in those who are severely infected and have preexisting vascular risk factors. Findings suggest that COVID-19 is an independent risk factor for acute ischemic stroke, particularly in young people (without typical vascular risk factors and only respiratory symptoms).

The pattern of large vessel occlusion and multi-territory infarcts suggests that cerebral thrombosis and/or thromboembolism could be possible causative pathways for the stroke.

Further studies are required to provide more robust estimates of the increase in stroke resulting from COVID-19 and to elucidate the precise pathophysiology linking COVID-19 to risk of stroke.

New models of care had to be developed to understand the highly infectious nature of the disease. Research has been hampered, but clinicians need to use the best available evidence to guide them in the management of their patients.

We hope the recommendations provided of experts will be of help to those involved in healthcare to develop treatment strategies and protocols even as we keep learning about COVID-19.

Stroke accident remains a diagnostic and therapeutic emergency during the crisis of COVID-19, and therefore, the adopting of guidelines and specific protocols to safely care for stroke patients is very important.

Guidelines regarding optimal care of stroke patients during COVID-19 pandemic are released by the American Heart Association and the American Stroke Association.

Abbreviation list:

COVID-19 = coronavirus disease 2019
SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2
CoVs = coronaviruses
S = spike protein
ACE-2 = angiotensin-converting enzyme 2

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