COVID-19 and Stroke: Incidental, Triggered or Causative

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Abstract

Stroke is a serious neurological comorbidity observed during the ongoing COVID-19 (coronavirus associated disease 2019) pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome, corona virus 2) and includes ischemic stroke, intracerebral haemorrhage and cerebral venous thrombosis. We reviewed factors that could potentially contribute to the occurrence of stroke among patients with COVID-19. There could be an interaction between the conventional risk factors of stroke, infection, systemic inflammatory response and plaque destabilisation. Inflammatory markers, D-dimer elevation and increased cytokine activity have been observed in patients with COVID-19. Other probable contributing factors include cardiac injury leading to embolism, a prothrombotic state and a possibility of direct neuroinvasive potential causing vasculopathy. Data from stroke patients gathered in large multicentric cohorts could help shed more light on the occurrence, behaviour, aetiology, pathophysiology, biomarkers and outcomes of stroke occurring during the ongoing pandemic.

Keywords: COVID-19, infection, SARS, SARS-CoV-2, stroke

Introduction

The current pandemic of COVID-19 or the severe acute respiratory syndrome caused by the novel corona virus (SARS-CoV-2) has led to a global health crisis. As on the day of submission of this manuscript, more than 3.5 million confirmed cases and 243401 deaths have taken place across the globe. One of the earliest clinical data published from Wuhan, China, described the clinical patterns and outcomes of 41 patients with COVID-19. The mean age of the patients was 49 years and they were predominantly males.[1] The presenting features were fever and cough in majority of the patients. ICU admission was required in 32% and 15% died. Following the initial description of this disease, there have been numerous publications on the nature of the virus, disease behavior, therapeutic options and guidelines to manage COVID-19. The aim of the review was to understand the putative pathways contributing to the occurrence of stroke among patients with COVID-19 and to explore a potential hypotheses related to it. We approached the review through many facets and relevant articles were searched, including the occurrence of neurological complications among patients with COVID-19, patient risk factors among the published reports of COVID-19, inflammatory response in COVID-19 as well as stroke, role of infection (s), neurotropism of coronaviruses, ACE 2 (angiotensin converting enzyme) pathway, cardiac injury in COVID-19 and a potential prothrombotic state in COVID-19. The present article aims to understand the potential relationship between COVID-19 and stroke.

Stroke occurrence in COVID-19 patients

Neurological involvement in COVID-19 patients has been recently published. Among 214 patients, 88 were observed to have some neurological symptom.[2] The authors classified them into central, peripheral and muscular features and included dizziness (36 [16.8%], headache (28 [13.1%]), hypogeusia (12 [5.6%]) and hyposmia (11 [5.1%]. Among these patients, cerebrovascular disease was observed in six, with ischemic stroke (IS) in five and intracerebral haemorrhage (ICH) in one patient. Patients with a more severe disease had a higher incidence of these events. In a report of 221 patients with SARS-Cov-2 infection, 13 (5.9%) patients developed stroke after a median duration of 10 days (IQR 1-29) of infection.[3] With the exception of a younger patient with cerebral venous thrombosis (CVT), the median age of this cohort was 73.5 years [IQR 57-91]). IS was seen in 11 (84.6%) patients and CVT and ICH in one each. The mortality was 38% among the stroke patients. Five patients were classified to have large vessel stenosis and three each were classified into small vessel disease and cardioembolic stroke. A very recent report describes five young patients with acute stroke during acute COVID-19 disease.[4] All presented with major intracranial vessel occlusion and had severe strokes treated with intravenous thrombolysis and/or endovascular treatment. Three patients had atherosclerotic risk factors and one of them

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had a previous stroke. Elevated D-Dimer levels were present in three patients. This suggests a complex relationship between conventional risk factors, infection and stroke and raises a concern about relatively younger patients developing a stroke during the ongoing pandemic; the cause and effect relationship, however, remains unclear.

Potential factors contributing to the occurrence of stroke in COVID-19

Cardiovascular disease, COVID-19 and stroke

Recent reports suggest cardiac involvement in COVID-19 patients.[5-7] Acute cardiac injury (suggested by the elevation of troponin), cardiac arrhythmias and heart failure have been reported,[6-8] although the likelihood of acute coronary events may also exist. A metanalysis of six studies observed cardiac injury in 8.0% patients, mostly occurring in patients who were sicker and in the ICU.[9] Possible mechanisms hypothesised include an acute inflammatory response, plaque destabilisation, direct myocardial injury, prothrombotic state, a higher metabolic demand etc.[5,6,10] This could potentially lead to a cardioembolic stroke either due to an altered myocardial function or an arrhythmogenic state or both.

Vascular risk factors among patients with COVID-19

Many reports have suggested age and comorbidities like hypertension, diabetes and cardiovascular disease to be associated with higher mortality in COVID-19.[1-3,7] In a recent report of patients with COVID-19 and stroke, five (38·5%) patients had a history of smoking and two (15.4%) patients had a history of alcohol intake.[3] Seven (53·8%) patients had increased blood pressure (≥130/80 mmHg) and 10 (76 9%) had elevated fasting blood glucose levels (>6·1 mmol/L) during admission to the hospital. Moreover, patients with stroke were more likely to have other underlying disorders, including hypertension (69·2%vs 22·1%, $P < 0·001$) and diabetes mellitus (46·2% vs 12·0%, $P < 0·01$).[3] A metanalysis of 1527 COVID-19 patients reported a 9.7%, 16.4% and 17.1% prevalence of diabetes, cardio-cerebrovascular disease and hypertension, respectively. The presence of risk factors like older age, hypertension, diabetes and previous cardiovascular-cerebrovascular disease is associated with increased disease severity, ICU stay[9] and death.[11-13] Underlying cerebrovascular-cardiovascular disease was present in 32% of patients who died versus 7.2% of survivors.[12] Another report from the Chinese Center for Disease Control and Prevention described a significantly higher mortality rate in patients with hypertension, diabetes and CVD (6%, 7.3% and 10.5%, respectively, versus an overall rate of 2.5%) among 44672 COVID-19 cases.[14] In a more recent metanalysis of 76993 patients, the pooled prevalence of hypertension, cardiovascular disease, smoking history and diabetes in patients with SARS-CoV-2 were estimated at 16.37% (95% CI: 10.15%–23.65%), 12.11% (95%CI 4.40%–22.75%), 7.63% (95%CI 3.83%–12.43%) and 7.87% (95%CI 6.57%–9.28%), respectively.[15]

Inflammatory response and risk of stroke

The relationship between inflammation and stroke is complex. Inflammation could directly or indirectly lead to the occurrence of stroke[16,17] or could follow an acute stroke.[18] Atherosclerosis is thought to be an inflammatory state that impairs the endothelial and smooth muscle functions,[19] leading to complications like plaque instability and vascular events. The biological interaction between inflammatory cells within the vascular wall and conventional risk factors, probably alters the dynamics of atherosclerosis. This has a potential to acutely worsen in the presence of systemic inflammation and effect the coagulation cascade.[16,19,20] Altered levels of soluble intercellular adhesion molecule (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), sE-selectin and TNF (tumour necrosis factor) alpha have also been observed in patients with hypertension.[17,21]

Inflammation within the plaque has been assessed using biomarkers, genetics, imaging (using plaque imaging as well as FGD-PET), the presence of infection or the response to anti-inflammatory agents.[16,17,20] CRP has traditionally been studied as a biomarker for inflammatory response and has been linked to stroke occurrence, severity, recurrence, outcomes and mortality.[22-24] A metanalysis by The Emerging Risk Factors Collaboration,[22] showed a positive relationship with circulating CRP and incident stroke and coronary disease in 160309 individuals without vascular disease. Among coronary artery disease patients, the predictive values of leukocyte counts, fibrinogen and CRP were comparable. The potential roles of aspirin and statin in secondary stroke prevention may partly be explained by their anti-inflammatory effect. Post stroke inflammation also contributes to a secondary brain injury, infarct edema and haemorrhage.[18] The release of cytokines contributing to tissue injury has been suggested and neuroprotectants have been tried with the premise of reducing inflammation after stroke.

Inflammation in patients with COVID 19: Implications for interactions with comorbidities and stroke

Inflammatory mediators have been implicated in the severity of SARS in COVID-19 and patients who developed a stroke showed an increased inflammatory response, including higher CRP levels, white blood cell and neutrophil counts, C-reaction protein levels and lower lymphocyte counts.[3] Cytokine levels have also been found to be higher among patients compared to controls and the levels of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A and TNFα were higher among ICU patients.[1] Studies have also documented low T cell fractions and higher IL10 levels as well as differential expression of cytokines and peripheral T cell subsets correlating with the severity of the disease.[25] The presence of high cytokine activity also brings in the possibility of an immune disarray and a potential role of immunomodulation. This intense cytokine activity could potentially induce heightened inflammation and dysregulation of thrombotic balance as well as vascular inflammation in already existing

plaques in the vessel wall. However, this needs to be proven with appropriate evidence.

COVID 19 and the prothrombotic state

Scientists have raised concerns of a prothrombotic state during the active COVID-19 illness. Data has shown increased levels of D-dimer in these patients[1,3]; whether this is a part of the sepsis or specifically related to a cascade of an inflammatory process is uncertain. It, however, raises concerns about the various pathways that could be contributing to the occurrence of cardiovascular complications. Amongst a small series of patients of severe pneumonia and ARDS, the authors reported benefit of intravenous thrombolysis using TPA (tissue plasminogen activator) in a pre-defined protocol.[26] A recent report of positive antiphospholipid antibodies among patients with COVID-19 suggests yet another potential pathway that could be responsible or may contribute to the occurrence of stroke in patients with COVID-19.[27]

COVID-19 and the ACE 2 pathway

SARS-CoV-2 virus enters the host cell using the ACE 2 receptor (angiotensin converting enzyme-2 receptor). ACE 2 is predominantly expressed by the epithelial cells of the lung, heart, kidney, blood vessels and intestine.[28-30] It is believed that ACE 2 has a higher affinity for angiotensin II and the cleaved products of angiotensin II (angiotensin 1–7) have effects opposite to angiotensin 2 itself, i.e., vasodilatation and cardio protection, the loss of which could potentially trigger cardiovascular and cerebrovascular events.[30] ACE 2 has also been found in brain and probably modulates autonomic responses.[31] The neurotropism of the virus could directly affect the nervous tissue and also modulate vascular response. A recent hypothesis sparked a concern that ACE inhibitors acting through ACE-1 (angiotensin converting enzyme-1) pathway could potentially make the illness worse by upregulating ACE-2 and allowing more entry of the virus into the host cell.[28] However, recent observations and expert opinions have disagreed with this concept and suggested continuation of the medications.[28,29]

Infection and stroke

The putative role of infection in stroke occurrence has been described for both ischemic stroke and ICH.[32] The process may either involve a direct invasion by the infecting agent, mediation through an inflammatory response or multiple interactions of various pathways. Inflammatory vasculopathy has been described with tuberculosis, syphilis, varicella zoster, fungal infections due to *Cryptococcus* and *Aspergillus*, HIV and some bacterial infections as well.[32-35] The invasion of the vessel wall could result from an inflammatory basal meningitis typically seen in tuberculosis or a direct invasion of vessel wall or both. Preceding infection could also trigger a stroke. Case control studies have suggested a relationship between a preceding urinary tract or respiratory infections and an increased risk of stroke over the ensuing days.[35] Using a large database, authors observed that the presence of any infection in the preceding two weeks is a potential trigger for stroke. The association was highest for preceding urinary tract infection (UTI) and ischemic stroke [OR 5.32 (95% CI, 3.69–7.68)] and a bit weaker for ICH [OR 1.80 (95% CI 1.04-3.11)].[36] The association between stroke and chronic infections with *Chlamydia pneumoniae* and *Helicobacter pylori* have also been evaluated using serological studies.[37,38] Using IgA, IgG and IgM antibodies against *C. pneumoniae*, authors have shown elevation of both IgG and IgA levels among patients with recent acute ischemic stroke compared to controls but correlation with IgA was significant.[37] *H. pylori* harboring the cytotoxin associated gene (cag A) is believed to be more strongly associated with stroke than the negative ones.[35,39] Postulated mechanisms underlying the occurrence of stroke with an incident infection include systemic inflammatory overactivity, prothrombotic state secondary to deficiency of protein C and S, increased arterial wall inflammation and worsening of atherosclerosis, immunological activity, cytokine excess, platelet overactivity and interactions between risk factors and infection.[32,33,35]

Viruses, Stroke and Role of Influenza

As mentioned above, viruses could be associated with the occurrence of stroke. Although many viruses, including HIV, EBV, HSV, CMV and HCV have been implicated,[32,33] the Varicella zoster virus has been most invoked in the occurrence of stroke especially in the paediatric and young population.[32,40-42] The risk of stroke is highest with an ophthalmic zoster. It is believed that the trans-axonal spread of the virus from the ganglion to the cerebral arteries, results in an arteritis due to a granulomatous inflammation and subsequent stroke.[41,42]

The process of vasculitis could also potentially occur with the coronaviruses causing SARS either due to a haematogenous involvement of the vessel wall or secondary to a direct neuroinvasive potential (see section below). Biological data to support this hypothesis is, however, needed. Exposure to respiratory illnesses has been associated with stroke occurrence.[35] The influenza group of viruses are the most common cause of endemic flu, especially the types A and B, and have been associated with neurological complications like GBS (Guillain–Barre Syndrome), ADEM (acute disseminated encephalomyelitis), encephalitis etc.[43,44] Reports of HINI infection and stroke have also been published previously in children.[45] The association between cardiovascular disease and influenza infection and a protective role of vaccination has been outlined previously in systematic reviews.[46,47] Vaccinations have not been observed to increase the risk of stroke, but respiratory infection itself potentially increases the risk of having a vascular event, especially in the first three days (incidence ratio of 4.95; 95% CI 4.43 to 5.53 and 3.19; 95% CI 2.81 to 3.62 for myocardial infarction and stroke, respectively).[48] In one large study, authors used information from the California State Inpatient Database of the Healthcare Cost and Utilization Project (HCUP).[49] Using a case series design, they analysed the occurrence of stroke with exposure to any "influenza like illness." The chances

of having an ischemic stroke were significantly increased in the first 15 days of exposure with infection (OR: 2.88, 95% CI: 1.86–4.47) and reduced as time from the index infection increased. Interestingly, the risk was higher among persons with a younger age.

Neuroinvasion by coronaviruses

Human coronaviruses (HCoV) have been previously associated with epidemic events including the SARS-CoV (severe acute respiratory distress) and the MERS-CoV (middle east respiratory distress) outbreaks.[50] HCoV-229E, HCoV-OC43 and SARS-CoV may possess neuroinvasive properties.[50,43] The human corona viruses have also been proposed to be related to chronic illnesses like multiple sclerosis especially in relation to the exacerbations.[51] The human blood–brain barrier (BBB) has the potential to prevent many infective agents from entering the CNS. However, many putative viruses have the capability of being neuroinvasive.[52] Theoretically, each virus could have this potential, but would depend upon many host- and agent-related factors. It could gain entry to the CNS either through a retrograde spread through the peripheral nervous system or through the haematogenous route. The animal corona viruses have been associated with nervous system affliction. One example of this is the mouse hepatitis virus (MHV), a subspecies of the murine coronavirus (MuCoV) which has significant neurovirulent properties.[53] The previously reported epidemics of SARS-CoV[54] and MERS-CoV (middle eastern respiratory syndrome)[55] have also observed neurological complications including occurrence of stroke. Autopsy specimens have also confirmed the presence of SARS-CoV in the human brain suggesting neurotropism.[56,57] However, limited reports are available as the severity of the outbreak was much lesser compared with the vastness of the ongoing COVID-19 pandemic. The murine coronaviruses could potentially gain entry into the CNS though the nasal olfactory route.[56] This is supported by the observation of anosmia as a symptom during the current ongoing COVID-19 pandemic.[58] ACE-2 receptor, the target for the virus to enter into the host cell, is believed to be present in the CNS.[30] Autopsy data on patients with SARS-CoV-2 have also given an insight into the invasive potential of the virus. In a recent series of autopsies on three patients with COVID-19 and multiorgan dysfunction, the authors reported the evidence of diffuse endothelial inflammatory reaction.[59] Although brain was not autopsied, a possibility of a similar process causing "endotheliitis" and vasculitis with secondary vascular occlusion cannot be excluded among patients with stroke and COVID-19. This could explain the occurrence of both ICH and ischemic stroke in this population. A recently reported case of acute meningoencephalitis in which the CSF was positive for SARS-CoV-2 virus and negative for nasopharyngeal swab could further suggest this host virus interaction.[60]

Management of Stroke Patients During COVID-19

Stroke management during COVID-19 could be challenging as it involves the pathways for rapid assessment and minimising delays at a time when the health systems could already be overwhelmed due to care of patients with COVID-19.[61-64] The screening processes during the triage needs to ascertain whether the patient is a COVID suspect and delineate pathways for timely treatment and minimum exposure to health care personnel. Suspects and positive patients will need to be treated in the COVID designated hospitals, which may make the treatment more challenging as the hospital may or may not be stroke ready. Within the hospitals, systems need to be in place, with separate corridors, pre-notification to the stroke team, availability of imaging, monitoring area and appropriate PPE for the healthcare personnel. Principles of stroke management and evaluation remain the same, but individualised decisions may need to be taken for patients seriously ill due to COVID-19.

Recently, guidelines to manage patients with acute stroke during COVID-19 have been published.[61-67] The concept of "protected stroke code" has been introduced to minimise delays and maximise safety during acute stroke management.[63] Anaesthesia care, endovascular stroke treatment and stroke management principles have been outlined to help assist the teams managing stroke.[65-68]

Building hypothesis of stroke and COVID-19

Occurrence of stroke among patients with COVID-19 seems multifactorial as evidenced by the above discussion [Figure 1]. Primarily, these patients seem to have underlying conventional risk factor (s). The presence of risk factors could predispose these patients to either develop an incidental stroke or the infective process could potentially trigger the same. One of the pathways could include the inflammatory and cytokine response, worsening plaque stability and thromboembolism. Another pathway is worsening cardiac function, precipitating a cardioembolic stroke either due to myocardial dysfunction or an arrhythmia. Downregulation of ACE-2 receptor may reduce the function of ACE-2 enzyme on angiotensin 2, leading to reduced activity of angiotensin,[1-7] produced as a cleavage and loss of cardioprotective and vasculo-protective functions. Evidence of a prothrombotic state is also emerging which could be contributing to stroke occurrence. Neurotropism and neuro-invasive potential of SARS-CoV-2 is being recognised. However, we still do not have an absolute proof that stroke is directly related to this process. A recent metanalysis of the published studies has suggested that patients with an underlying cerebrovascular disease are at a higher risk of developing more severe COVID-19.[69] Presumably, such patients have comorbidities, vascular risk factors and are relatively older and, therefore, also at an increased risk of having a recurrent stroke.

Future direction and clinical applications

Data from stroke patients gathered in large multicentric cohorts could help shed more light on the occurrence, behaviour,

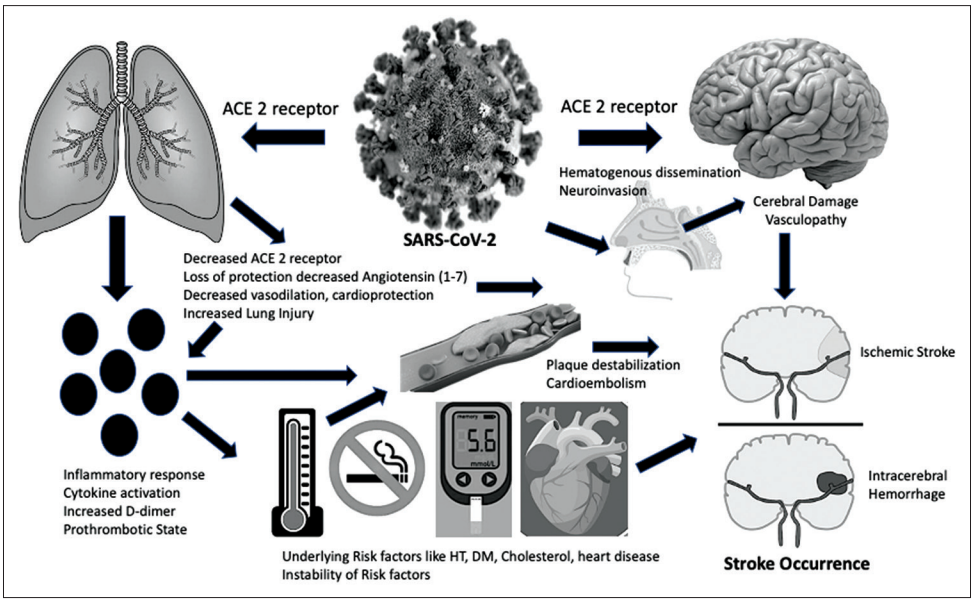

Figure 1: Potential mechanisms of stroke in COVID-19. The virus could haematogenously disseminate or invade the nervous tissue through the olfactory pathway. ACE-2 receptor may help attach the virus to the neuronal tissue and elicit a cascade of neuronal damage or vasculopathy. The systemic inflammation may cause tissue or vascular wall damage and plaque destabilisation. The ACE-2 receptor may get downregulated and may cause decreased activity of ACE-2 enzyme that cleaves the protective angiotensin 2 to angiotensin 1–7 fragment, the loss of which may induce the risk of stroke

aetiology, biomarkers and outcomes of stroke patients seen during the ongoing pandemic. Interestingly, knowing how many patients are asymptomatic for COVID-19 and present with an incidental stroke is equally important to establish a relationship of association or causation. This is an important time to understand and take the hypothesis forward to understand the pathogenesis. We must be prepared to handle the complications in the ongoing pandemic and an effective understanding of stroke behaviour and its causation would be critical. Treatment of COVID-19 with an effective modality, thereby reducing cascade of inflammatory events may seem a way forward to reduce the occurrence of an incidental stroke during COVID-19 infection.

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Conflicts of interest
There are no conflicts of interest.

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