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Novel Corona Virus and acute ischemic stroke – An Over view

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ABSTRACT

The COVID-19 pandemic represents an unprecedented global healthcare challenge. Aside from being a primary respiratory disease, acute ischemic stroke has emerged as a complication of the disease. There are many similarities in the risk factors for severe COVID-19 as well as ischemic stroke, which underscore the complex relationship between these two conditions. Acute ischemic stroke in patients with COVID-19 may be due to usual causes such as atherosclerosis, hypertension, and atrial fibrillation. Approximately 5% of hospitalized patients with covid -19 suffer from stroke with over 80% of them being ischemic stroke. Rapid assessment and time-sensitive interventions required for optimum outcomes in acute stroke care have been complicated by COVID-19. In this review, however, we focus on mechanisms of stroke that appear to be directly related to COVID-19, the clinical features of COVID-19 patients who develop ischemic stroke, and in addition we have discus the management approaches of acute ischemic stroke in COVID-19 patients.

Keywords:COVID-19, Acute Ischemic stroke, ischemic stroke management, vasculitis, cardiomyopathy

INTRODUCTION

The novel corona virus has quickly become widespread, resulting in an epidemic throughout China, followed by a pandemia, with an increasing number of cases in various countries throughout the world.[1] Although COVID-19 is primarily a respiratory illness, reports suggest that it may lead to a hyper-coagulable state and thrombotic complications. Recent publications from China, France, and New York raise the possibility that COVID-19 might increase the risk of acute ischemic stroke.[2]Since the beginning, the link between COVID-19 and ischemic stroke has been increasingly documented in recent literature and mass media, be it in young COVID-19 patients or patients without pre-existing cardiovascular risk factors or significant comorbidities.[3]. Many facets and relevant articles related to covid-19 and its complications were searched, including the occurrence of neurological complications among patients with COVID-19, patient risk factors among the published report of COVID-19, inflammatory response in COVID-19 as well as stroke, role of infections, neurotropism of corona viruses, ACE 2 (angiotensin converting enzyme) pathway, cardiac injury in COVID-19 and a potential prothrombotic state in COVID-19. The present aim of the article is to understand the potential relationship between COVID-19 and acute ischemic stroke.[4]Three main mechanisms appear to be responsible for the occurrence of ischemic strokes in COVID-19. These include a hypercoagulable state, vasculitis, and cardiomyopathy.

HYPERCOAGULABLE STATE

Lee et al, in their study, reported that 20–55% of patients hospitalized with COVID-19 have laboratory evidence of coagulopathy, with increased levels of D-dimer to above twice normal, slight prolongation of prothrombin time (1–3 s above normal), mild thrombocytopenia, and in late disease, decreased fibrinogen levels. A D-dimer level above 4 times normal was associated with a 5-fold increase in the

likelihood of critical illness.[5]The underlying pathophysiology contributing to the hypercoagulable state in covid-19 patients may be related to Disseminated intravascular coagulation (DIC), properties of the virus itself, antiphospholipid syndrome, activation of the complement cascade, and endothelial dysfunction induced by the infection.[6]SARS-CoV-2 mortality has been linked to a dysregulated inflammatory reaction, likely from a cytokine storm or macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistocytosis. Mc Gonagle et al. in their study stated, that the tropism of SARS-CoV-2 towards angiotensin-converting enzyme 2 (ACE2), mostly present in type II pneumocytes, leads to an inflammatory cascade causing a generalized pulmonary hypercoagulablestate. The secondary lymphohistiocytosis triggers expression of tissue factor in the endothelial cells, macrophages, and neutrophils, inducing activation of the coagulation cascade. Beyond the hypercoagulable state this generates, a study of bronchoalveolar lavage showed that both severe pneumonia and acute respiratory distress syndrome (ARDS) are associated with thrombin generation and fibrin deposition within the bronchoalveolar system. [7]

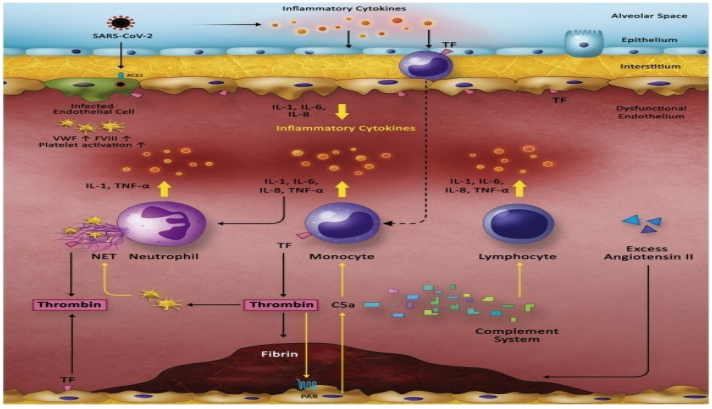

Fig: 1. Pathophysiology of the Hypercoagulable State in COVID-19.

COVID-19 leads to a severe inflammatory response that originates in the alveoli. Release of inflammatory cytokines leads to activation of epithelial cells, monocytes and macrophages. Direct infection of the endothelial cells through the ACE2 receptor also leads to endothelial activation and dysfunction, expression of TF, and platelet activation and increased levels of VWF (von Will brand factor) and FVIII, all of which contribute to thrombin generation and fibrin clot formation. Thrombin, in turn, causes inflammation through its effect on platelets which promote NET formation in neutrophils. It also activates endothelium through the PAR receptor, which leads to release of C5A that further activates monocytes.[8]

VASCULITIS

Recent studies have shown that the virus not only affects the respiratory system but also various other systems, which brings about a new dimension to the pathogenesis of COVID-19. SARS-COV-2 is well known to affect the lungs causing symptoms such as dry cough, dyspnoea, fever, intense inflammatory response, and cytotoxic response.[9] Other clinical examination shows bilateral ground-glass opacities, increased levels of C-Reactive Protein, and Erythrocyte sedimentation rate. Severe cases may develop to thromboembolic and atheroembolic incidents leading to stroke.[10]The virus enters the host through the Angiotensin-Converting Enzyme 2 receptor which is well furnished with the epithelial and endothelial cells. The hypothesis states that the virus affects the endothelial cells which are present all over the body especially in the blood vessels. Thus, vacuities becomes an important part of the pathogenesis of COVID-19.[9,10] Zsuzsanna Vargaetal, has reported a few cases that involve endothelial dysfunction and apoptosis.The histological findings clearly show that SARS-COV-2 induces endotheliitis in several organs due to the presence of viral elements and host inflammatory response. Further, it induces apoptosis and pyro-ptosis which plays a major role in epithelial cell injury.[11]Vasculitis has been declared as a clinical symptom of SARS-COV-2 due to endothelial damage and increased levels of anti-phospholipids which has been observed in some patients with thrombosis. Apart from this, lymphocyte infiltration, enlargement, and narrowing of blood vessels also contribute to the mechanism of vasculitis in SARS-COV-2 patients.[12]Roncati et al. has stated that the SARS-COV 2 has an upsurge from humoral immunity to immune complex disease (type 3 hypersensitivity) with the deposition of antigen-antibody complexes inside the blood vessels, inducing an inflammatory response, sequentially stimulating the release of histamine and phagocytes which causes tissue damage. The outcome of this process is described as leukocytoclastic vasculitis.[13]Ackermann et al. scrutinized the lung autopsy of 7 SARS-COV-2 patients and compared them with 7 influenza patients. They observed 3 marked perivascular features in SARS-COV-2 patients. The first feature being, serious endothelial damage due to the presence of viral bodies inside the cell. The second, widespread vascular thrombosis with microangiopathy and obstruction of capillaries in the alveoli. Third, the formation of new vessels by intussusceptive (non-sprouting) angiogenesis.[14]Harlan M et al. has reported a case of a 31yr old woman with heart complications after 2 weeks of discharge due to SARS-COV-2. Her autopsy reported endotheliitis and vasculitis of the small vessels in the heart.[15] RyoheiOda et al. has

reported a case on Large Vessel Vasculitis (LVV) after SARS-COV-2 infection. Their findings on CT and 18F-flurodeoxyglucose positron emission tomography (18F-FDG PET/CT) showed elevated 18F-FDG uptake in the arterial wall where increased contrast enhancement had been observed. This finding helped in the diagnosis of LVV associated with SARS-COV-2.[16] These reports show that cardiac small vessel vasculitis and large vessel vasculitis could be a late complication of SARS-COV-2.SARS-COV-2 is known to affect the brain hemostasis by crossing the blood-brain barrier causing inflammatory damage or ischemic stroke. [17]Gustavo et al. reported a case involving neurological examination of the patient whose serum serological test showed SARS-COV-2 IgM positive. The findings of the MRI brain revealed two hyperintense lesions in cortical and subcortical regions, possibly due to vasculitis. [18] Hanafi R et al. had also reported a case on a definite neurogenic complication of SARS-COV-2 with extensive ischemic lesions resembling CNS vasculitis. Neuroimaging findings depict injury to the small intracranial vasculature of distal perforating arteries and extensive ischemic lesions with restricted diffusion.[19]

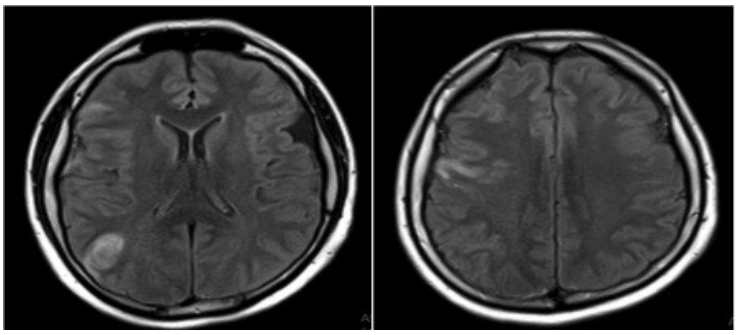

Fig: 2. MRI image demonstrates FLAIR sequence with two hyperintense

Figure: 2. MRI image demonstrates FLAIR sequence with two hyperintense lesions in right parietal and frontal areas at subcortical region, with diffusion restriction. Also, it is possible to note Arachnoid cyst in right temporal fossa. Conclusions: Two hyperintense lesions in cortical and subcortical regions, possibly due to vasculitis.[18] Dermatological changes have also been linked to SARS-COV-2. The changes include chilblains, urticaria-like lesions, livedoreticularis, erythema which present with different forms of vasculitis.[20,21]The exact mechanism of skin invasion by SARS-COV-2 is unclear but several theories have been postulated, such as activation of keratinocytes due to inflammatory response, circulating immune complex inducing vasculitis, and reduced blood flow to the microvasculature of the skin.[22] Perosanz-Lobo et al. reported two cases of erythematous patches. The histopathological findings revealed characteristics of small-vessel vasculitis. This finding suggests the presence of urticarial vasculitis.[23] Juan et al. reported erythema-multiform like lesions during hospitalization and even after discharge. Histological changes showed dilated vessels filled with neutrophils and lymphocytic perivascular and interstitial infiltrate. [24]

CARDIOMYOPATHY

Numbers of mechanisms are there for cardiac involvement in COVID-19 patients. . Zhou et al, reported that heart failure was observed in 23.0% of patients with COVID-19 presentations.There may be direct invasion by the virus, causing a myocarditis, with resultant injury and even death of cardiomyocytes. Myocardial injury, as defined by an increased troponin level, can occur due to myocardial ischemia or nonischemic myocardial processes including myocarditisWith severe respiratory infection and hypoxia, especially in the setting of severe infection and ARDS due to COVID-19, it is likely that a number of patients will develop such injury. High prevalence of arrhythmia might be, in part, attributable to metabolic disarray, hypoxia, or neurohormonal or inflammatory stress in the setting of viral infection in patients with or without prior CVD.[25] 7% of COVID-19–related deaths were attributable to myocarditis. Patients with comorbid condition of cardiovascular diseases are at increased risk for myocardial injury. It was also mentioned that performing laboratory investigations related to cardiac studies, such as troponin 1 levels, creatinine kinase MB, N-Terminal-pro-Brain Natriuretic Peptide (NT-pBNP) and ECG would help in early detection of acute myocardial damage. [26] A review article by European society of cardiology (ESC) recommended cardiac magnetic resonance (CMR) imaging for suspected acute myocarditis. Diagnosis of acute myocarditis can be done by cardiac magnetic resonance imaging (MRI) and Endomyocardial biopsy (EMB),that can directly demonstrate myocyte necrosis and mononuclear cell infiltrates. [27] Cardiac CT angiography can be used as a non-invasive imaging tool for patients with suspected coronary artery disease, in which non-contrast enhanced CT is usually recommended forCOVID-19 patients to reduce the risk of virus transmission through intravenous contrast injection.[28] Baseon the studies, Q.deug et al.,divided the patients in two groups, non-severe groups (mild and moderate types) and severe group (severe and critical types). Severe type patients were presented with one of the three criteria that is respiratory distress and respiratory rate higher than 30 times per minute; fingertip blood oxygen saturation below 93% at rest; partial arterial oxygen pressure (PaO2)/fraction of inspiration oxygen (FiO2) below 300 mmHg. Critical type patients were presented with one of these three criteria: respiratory failure, requiring mechanical ventilation; shock; multiple organ failure, thereby requiring intensive care management. He also proposed that there was a raise in the

troponin 1 levels after hospitalization in severe patients along with an increase in CK-MB and NT-pro-BNP. [29] The pathophysiology of SAR-CoV-2 on cardiomyopathy shows that, virus enter into human cells by binding its spike protein to the membrane protein angiotensin converting enzyme 2 (ACE2).The S-glycoprotein receptor present on the surface of the virus possesses two subunits, S1 and S2, which attach to the ACE2 receptor. S1 determines the virus host range and cellular tropism, whereas S2 initiates fusion of the virus-cell membrane. But before its binding, the virus undergoes a process of cleavage by a serine protein called TMPRSS2. ACE2 can be found on the ciliated columnar epithelial cells of the respiratory tract, type II pneumocytes, and cardiomyocytes. Therefore, it is plausible that SARS-CoV-2 infects the human heart, especially in case of heart failure as ACE2 is up regulated.[30] Myocardial injury in covid -19 patients, may be due to Cytokine release syndrome (aka 'cytokine storm'), that is caused by activation of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, T helper 1 cytokine interferon-gamma, and tumour necrosis factor-alpha (TNF-α). Proinflammatory cytokines depress myocardial function by activating neural sphingomyelinase pathway and subacutely (hours to days) via nitric oxide thereby reducing the action of beta-adrenergic signaling.[31]

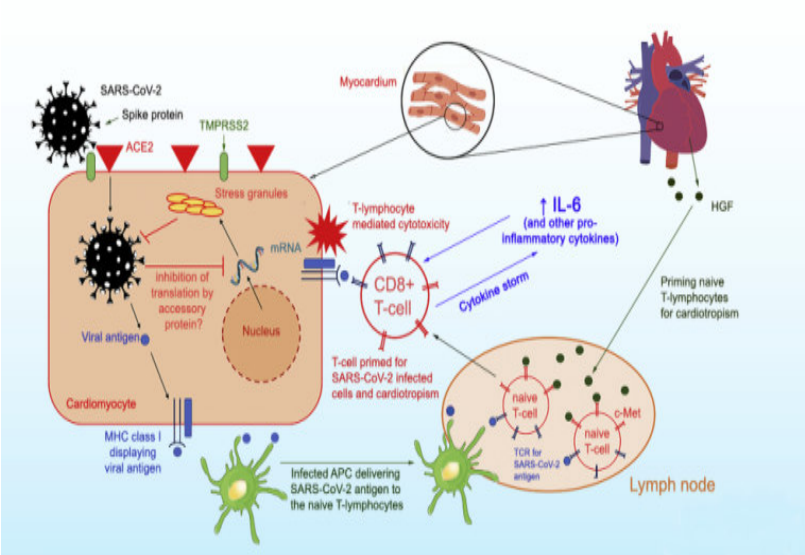

Fig: 3 Proposed pathophysiology of SARS-CoV-2 myocarditis.

SARS-CoV-2 utilizes the spike protein (primed by TMPRSS2) to bind ACE2 to allow cell entry. Intracellular SARS-CoV-2 might impair stress granule formation via its accessory protein. Without the stress granules, the virus is allowed to replicate and damage the cell. Naïve T lymphocytes can be primed for viral antigens via antigen-presenting cells and cardiotropism by the heart-produced HGF. The HGF binds c-Met, an HGF receptor on T lymphocytes. The primed CD81 T lymphocytes migrate to the cardiomyocytes and cause myocardial inflammation through cellmediated cytotoxicity. In the cytokine storm syndrome, in which proinflammatory cytokines are released into the circulation, T-lymphocyte activation is augmented and releases more cytokines. This results in a positive feedback loop of immune activation and myocardial damage. ACE2 5 angiotensinconverting enzyme 2; APC 5 antigen presenting cell; HGF 5 hepatocyte growth factor; IL-6 5 interleukin 6; MHC 5 major histocompatibility complex; SARS-CoV-2 5 severe acute respiratory syndrome coronavirus 2; TCR 5 T-cell receptor.[31]

MANAGEMENT OF ACUTE ISCHEMIC STROKE IN COVID-19

A single center study, which was conducted on 221 consecutive hospitalized patient with COVID-19 infection reported that 11 (5%) developed acute ischemic stroke, 1 (0·5%) cerebral venous sinus thrombosis, and 1 (0·5%) cerebral hemorrhage. The mean age of patients who developed stroke (72 years) was higher (52 years) and the stroke group had higher frequency of hepatic and renal dysfunction. The frequency of hypertension, diabetes mellitus, and previous history of cerebrovascular disease were higher among those who developed stroke. [32]The fibrin D-dimer levels were 12-fold higher in patients who developed stroke indicating a hypercoagulable state. Cerebrovascular events were found to be more common in older patients with stroke risk factors such as hypertension and diabetes mellitus, and those who had elevated fibrin D-dimers.[33]

ANTICOAGULATION, THROMBOLYSIS AND MECHANICAL THROMBECTOMY

As ischemic stroke can occur in a systemic prothrombotic state under COVID-19 infection All patients admitted to intensive care should receive prophylaxis against venous thrombosis, with at least LMW heparin. Tang et al., reported that anticoagulation reduced mortality in COVID-19 patients with coagulopathy. [5]Asakura and Ogawa noted that some features of the coagulopathy in

COVID-19 suggest DIC and recommended a combination of heparin and nafamostatmesylate, a treatment used for DIC in Japan. [34] The efficacy and safety of anticoagulants in patients with COVID-19 requires the comprehensive judgment of TOAST classification, clinical syndrome, National Institutes of Health Stroke Scale (NIHSS) score, and laboratory findings. [35] Current guidelines recommend commencing intravenous thrombolysis with rt-PA within 3 hours of stroke onset and within 3 to 4.5 hours in selected patients. Hepatic dysfunction manifesting with elevated transaminases as well as coagulopathy is documented abnormalities in COVID-19. [36] Thrombectomy also plays a crucial role in treating acute stroke patients.Yaeger et al., in their study reported 10 patients with large vessel occlusion undergoing thrombectomy with a successful reperfusion rate of 90% and concluded that thrombectomy continues to be an effective therapy. [37]The case series from the UK also supports early therapeutic anticoagulation with LMWH for better prognosis in severe COVID-19 patients meeting sepsis-induced coagulopathy criteria or with markedly elevated D-dimer.[38]

INTUBATION AND MECHANICAL VENTILATION

Patients with COVID-19 infection may be at higher risk for intubation because of respiratory failure with almost 20% having hypoxic respiratory failure. A low threshold for initiating intubation, mechanical ventilation, and general anesthesia may be required in patients with COVID-19 infection who are selected for mechanical thrombectomy to reduce exposure risk during procedure by maintaining ventilation through closed circuit and avoiding unplanned intubations. [39]

ANTI-INFLAMMATORY THERAPIES

Cardiovascular protective strategies are urgent for the prevention and management of severe adverse cardiovascular events, which is of great significance to the overall prognosis of COVID-19 patients. Excessive inflammation should be considered as a promising target because There is an abundant evidence that inflammation participates in various cardiovascular diseases, such as coronary artery disease (CAD) and HF. Anti-inflammatory drugs which has been proved in cardiovascular clinical trials, such as IL-6R monoclonal antibodies (tocilizumab), TNF-α inhibitors (etanercept and infliximab), and IL-1β antagonists (the monoclonal antibody canakinumab and the anti-cytokine anakinra) used for treating patients with COVID-19.[40]

ANTIVIRAL THERAPY

Many clinical trials are currently underway to evaluate the efficacy of anti viral drugs on the outcome of COVID-19 patients, but their results have not been published yet. Suggested anti viral drugs in the treatment of COVID-19 includes, remdesivir, Lopinavir-ritonavir combination,Ribavirin,Favipiravir, Umifenovir.[41 42]

CONCLUSION

Stroke is an important neurovascular complication of SARS-CoV2 infection, involved a number of mechanisms including a hypercoagulable state, DIC, necrotizing encephalopathy, vasculitis, and cardiomyopathy. Hypercoagulation markers such as D-dimer are substantially elevated among all patients early in the disease progression. Older patients with severe disease are at a higher risk of this complication, but large-vessel occlusion is being commonly reported in younger patients. Rapid assessment and intervention required for optimum outcomes in hyperacute stroke in COVID-19. Proper education including stroke awareness and COVID-19 knowledge is absolutely essential during this pandemic. The awareness gained by these difficult time must propel us to carefully and proactively plan for the future, so that the crucial role of neurology in managing neurological emergencies and chronic disease is safeguard and optimized.

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