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Impact of COVID-19 on the cerebrovascular system and the prevention of RBC lysis

N. AKHTER[1], S. AHMAD[2], F.A. ALZAHRANI[3], S.A. DAR[4], M. WAHID[4], S. HAQUE[4], K. BHATIA[5], S. SR ALMALKI[1], R.A. ALHARBI[1], A.A.-A. SINDI[1]

[1]Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University, Albaha, Saudi Arabia
[2]Department of Neurosurgery, Barrow Neurological Institute, St Joseph's Hospital and Medical Center, Phoenix, AZ, USA
[3]Department of Biochemistry, Faculty of Science, Stem Cells Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[4]Research and Scientific Studies Unit, College of Nursing and Allied Health Sciences, Jazan University, Jazan, Saudi Arabia.
[5]School of Mathematical and Natural Sciences, Arizona State University, Phoenix, AZ, USA

Naseem Akhter, Saif Ahmad and Faisal A Alzahrani contributed equally

Abstract. – Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) uses Angiotensin- converting enzyme 2 (ACE2) receptors to infect host cells which may lead to coronavirus disease (COVID-19). Given the presence of ACE2 receptors in the brain and the critical role of the renin-angiotensin system (RAS) in brain functions, special attention to brain microcirculation and neuronal inflammation is warranted during COVID-19 treatment.

Neurological complications reported among COVID-19 patients range from mild dizziness, headache, hypogeusia, hyposmia to severe like encephalopathy, stroke, Guillain-Barre Syndrome (GBS), CNS demyelination, infarcts, microhemorrhages and nerve root enhancement.

The pathophysiology of these complications is likely via direct viral infection of the CNS and PNS tissue or through indirect effects including post- viral autoimmune response, neurological consequences of sepsis, hyperpyrexia, hypoxia and hypercoagulability among critically ill COVID-19 patients.

Further, decreased deformability of red blood cells (RBC) may be contributing to inflammatory conditions and hypoxia in COVID-19 patients. Haptoglobin, hemopexin, heme oxygenase-1 and acetaminophen may be used to maintain the integrity of the RBC membrane.

Key Words:
SARS-CoV2, Cerebrovascular system, RBC lysis.

Introduction

Current SARS-CoV2 pandemic has caused a total of 20,439,814 cases with 744,385 deaths globally[1]. SARS- CoV2 belongs to the same family of viruses responsible for 2003 SARS pandemic (8422 infected cases and 916 deaths globally)[2] and the outbreak of MERS (2519 cases and 866 deaths globally)[3]. Despite having low mortality rate, SARS-COV2 is causing higher number of deaths than previous two outbreaks owing to an increased infectivity and higher transmission potential[4].

Coronaviruses (CoVs), single-stranded RNA viruses of the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae[5], are classified into four major groups: α- CoVs, β- CoVs, γ- CoVs, and δ- CoVs with 17 subtypes[6]. Primarily infecting wild animals, CoVs can also infect humans presumably owing to the mutation in the key regions of genome like large deletions in the open reading frame 8 (ORF8) region and mutations in the spike (S) protein. These mutations resulted in the human adaptation of virus infecting upper and lower respiratory tract[5] leading to 2002 SARS outbreak[7].

The exponential rise of COVID-19 globally has made the treatment extremely difficult. Patients having comorbidities like cardiovascular diseases, hypertension, diabetes, chronic kidney disease are at significantly high risk of worsening the disease[8]. Previous MERS-CoV infection exacerbated the underlying conditions like hypertension leading to chronic organ damage[9]. Having similar pathogenicity, SARS-CoV2 infection can also progressively deteriorate the symptoms in patients with comorbidities.

Corresponding Author: Naseem Akhter, Ph.D; e-mail: nakhter@bu.edu.sa; naseem.du@gmail.com

Neurological Complications of SARS-CoV2 Infection

The primary focus in ongoing pandemic is on acute respiratory distress syndrome (ARDS) symptoms, however, emerging evidence warrants an improved understanding of associated neurological complications like encephalopathy[10], meningo-encephalitis[11], ischaemic stroke[12], acute necrotizing encephalopathy[13], and GBS[14].

Early in pandemic, reports of dizziness, headache, hypogeusia, and hyposmia in almost 37% of 214 COVID-19 hospitalized patients indicated involvement of nervous system. However, complications like stroke and loss of consciousness were largely limited to the severely ill patients[15].

By mid-May, reports of central nervous system (CNS) demyelination, infarcts, microhemorrhages, features of posterior reversible encephalopathy syndrome, or nerve root enhancement began to appear. These extra pulmonary complications are possibly caused by direct viral neuronal injury[16] and a secondary hyperinflammation syndrome[17]. Additionally, inflammatory or immune-mediated disorders, neurological consequences of sepsis, hyperpyrexia, hypoxia, hypercoagulability are also contributing to pathogenesis[18,19].

The neurological complications of SARS-CoV2 have similarities to those described in previous coronavirus epidemics, specifically severe acute respiratory syndrome (SARS) in 2003, and Middle East acute respiratory syndrome (MERS) in 2012. Those reports included encephalopathy, encephalitis and both ischemic and hemorrhagic stroke caused by hypercoagulability, sepsis, vasculitis, and GBS[20-22]. However, the total numbers of patients were smaller and neurological presentations were few in comparison with those being witnessed in the current pandemic.

Early reports of the neurological complications in COVID-19 patients included loss of smell and taste leading to stroke in almost 3% of the cases[15]. Severe systemic illnesses like sepsis and hypoxia were speculated the reason behind the loss of smell and taste. However, more recent reports show neurological complications like ischemic stroke, perfusion changes, myoclonus[23] and demyelination[24] (Figure 1).

Direct Impacts of SARS-CoV-2 on the Nervous System

Headache, nausea, vomiting[25], anosmia[26], ageusia[27] and myalgia[8] are the most common and early symptoms of neurological involvement. Generally mild headache, caused by direct infection of nervous system by SARS- CoV- 2, may lead to the loss of consciousness in the critically ill COVID-19 patients. Anosmia and ageusia generally reported together[27,28] in almost two thirds of mildly ill COVID-19 patients, are possibly caused by infection of oral mucosa by SARS- CoV- 2[29]. Brann et al[30] showed that SARS-CoV-2 infection of non-neuronal olfactory epithelial sustentacular cells and olfactory bulb pericytes, and not infection of olfactory sensory neurons is responsible for anosmia in COVID-19 patients.

Myalgia (muscle pain), observed in almost half of the COVID-19 patients[31], may worsen into rhabdomyolysis affecting renal and muscle enzymes leading to kidney failure[32].

Acute necrotizing encephalopathy causes hemorrhage in thalami, medial temporal lobes and subinsular regions which may lead to multiple organ failure, hypoxemia, systemic inflammation and endothelialitis in critically ill with co-morbidities[13].

Similarly, an increased risk of stroke is also associated with co-morbidities in critically ill COVID-19 patients[21]. Changes in coagulability and blood vessels along with hypoxia increase the risk of stroke of both arterial and venous cerebrovascular origin[28,33-35].

Frequent cerebral microbleeds in stroke among COVID-19 patients are probably caused by the extravasation of red blood cells and direct infection of endothelial cells leading to endothelial dysfunction[36,37]. Furthermore, thrombosis, pulmonary embolism, significantly high D-dimer levels, along with abnormal coagulation parameters indicate poor prognosis[38].

COVID-19 and Ischemic Brain Injury

Diffused alveolar and interstitial inflammatory exudation, edema and the formation of transparent membranes cause impaired alveolar gas exchange and create hypoxia in the CNS after viral infection[39]. Hypoxia further interrupt the blood brain barrier (BBB) and cause ischemic stroke, neuronal, glial, and vascular injury involving critical complement cascade considering immune and inflammatory axes[40].

Cerebral edema and the cerebral circulation disorder worsen in the event of persistent hypoxia. A recent report shows that COVID-19 patients often suffer from severe hypoxia[41] which can also induce neuronal cell death and BBB dysfunction via activation of inflammatory and cytotoxic molecules along with oxidative stress signaling[42,43]. Importantly, ischemic injury not

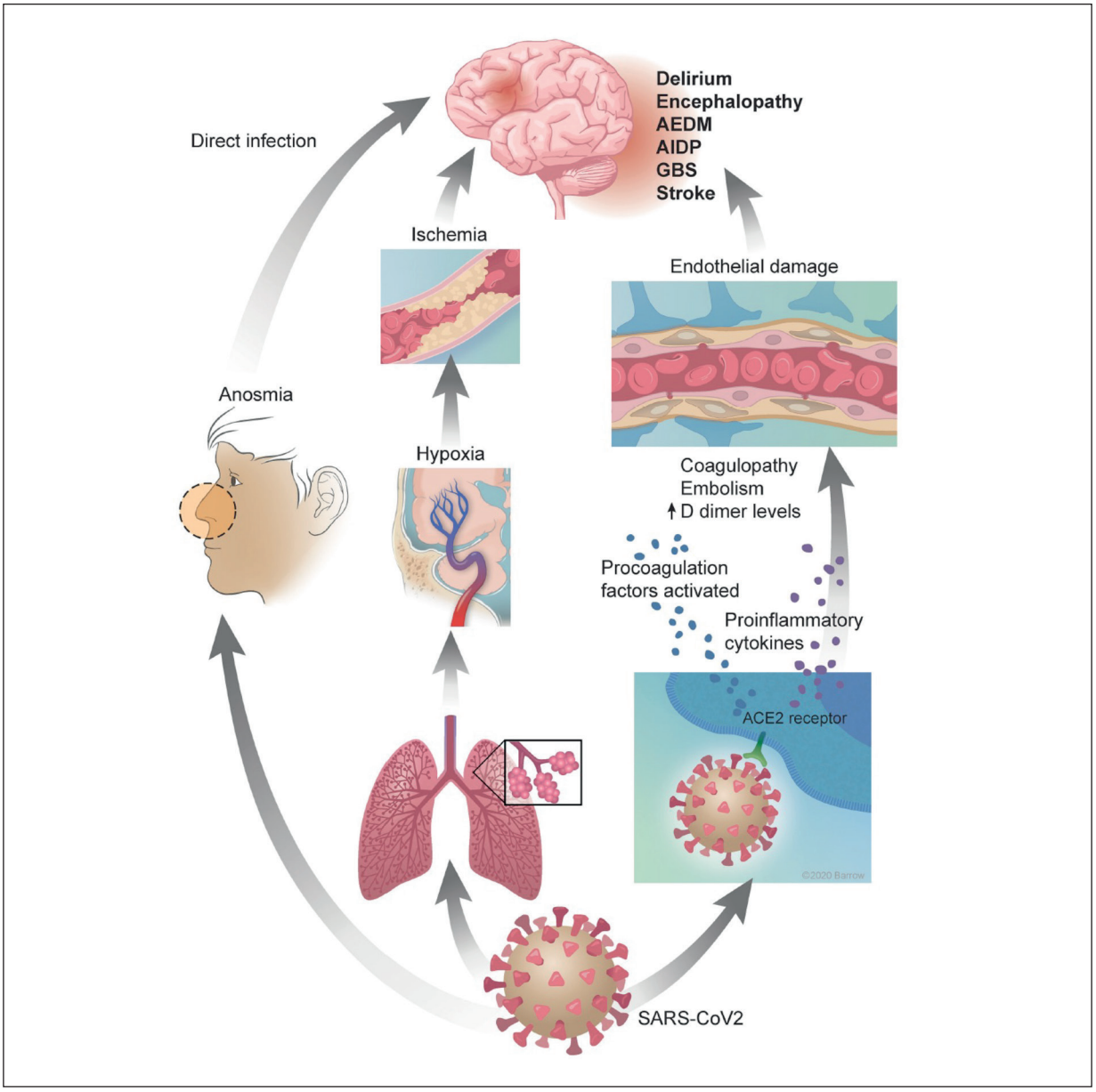

Figure 1. SARS-CoV-2 virus causes a host of neurological complications via direct viral infection of nervous system or indirectly through sustained pro inflammatory status, sepsis, thromboembolism, and damage to blood brain barrier.

only causes death of brain endothelial cells but also atherosclerosis, hemorrhage, brain edema, and vascular dementia[44-47].

Immune and Inflammatory Response Causing Neurological Complications

Viral infections generally trigger an immune inflammatory response damaging the nervous system through acute disseminated encephalomyelitis (ADEM) and acute inflammatory demyelinating peripheral neuropathy (AIDP)/ Guillain-Barre syndrome. Early studies have shown the association of MERS infection with encephalitis and GBS[22]. More recently, human corona virus infection, other than SARS, has been found to be associated with Guillain-Barre syndrome with unilateral peripheral facial and bulbar palsy[48]. Early reports of current pandemic indicated the presence of transverse myelitis among hospitalized COVID-19 patients in Wuhan, China[49].

Of late, report of GBS at 0.41% are rare and miniscule[14] when compared with expected incidence of 0.6–2.7/100 000/year[50] warranting further epidemiological studies to confirm a COVID-19 associated increase in GBS incidence.

Current reports are also showing presence of transient encephalopathies with delirium, psychosis and cognitive dysexecutive syndromes[36,51]. However, the magnitude of cognitive dysfunction and other psychiatric and psychological factors during recovery remains to be studied[52].

Another recent article discusses cases of possible autoimmune encephalitis, clinically similar to opsoclonus and myoclonus[36,53]. Surprisingly, NMDAR and LGI1 autoantibodies were not found in the patient's sample indicating that SARS-CoV-2 may induce autoimmune encephalitis.

Further, rare acute disseminated encephalomyelitis (ADEM) typically found in children has earlier been reported caused by the human coronavirus OC43 infection[54] and thus its occurrence was not entirely unexpected during the current pandemic. The first report was a non– peer reviewed article showing acute flaccid paralysis of the bilateral lower limbs and urinary and bowel incontinence in 66-year-old man[55]. The clinical findings indicated post-infectious acute myelitis; however, infection of spinal cord neurons was also suspected[55].

A latest report indicates the association of COVID-19 with an increased incidence of ADEM, however, clinical findings showed an absence of SARS-CoV-2 in CSF and brain tissue suggesting post-infectious disease mechanism[36].

SARS-CoV2 and ACE2

ACE2, a functional receptor for coronaviruses[56], is aminopeptidase enzyme present on the cells in the lungs, arteries, heart, brain, kidney, and intestines[57,58]. ACE2 reduces blood pressure by catalyzing the cleavage of angiotensin II (a vasoconstrictor peptide) into angiotensin (1-7) (a vasodilator)[59-61] and thus has a critical role in the onset and development of hypertension. ACE2 presence in the cerebral cortex, striatum, hypothalamus, and brainstem greatly increases the risk of direct CoV infection[62].

MERS- CoV experience has clearly established the hypertension along with diabetes mellitus, chronic lung disease, heart disease, and smoking as comorbidities associated with not only primary infection risk but also poor prognosis[63,64].

A recent genetic study has shown the spatial correlation of ACE2 gene with several genes associated with the organs affected in COVID-19. The findings of the study suggest that direct viral invasion of brain using ACE2 affects brain regions related with esophagus, thyroid, spleen, lymph node, bone marrow, testis, ovary, uterus, and heart functions[65].

COVID-19 and the Regulation of Adaptive immune response

The immune and nervous system, both acts synergistically to respond to the threat faced by the body. Cytokines contribute critically to the normal brain development and various neurological disorders through an upregulated cytokines production by T lymphocytes. Further, adaptive immune response is largely regulated by the balance between mutually exclusive pro-inflammatory Th1 and anti-inflammatory Th2 cytokines. While Th1 cells activation contributes to CNS inflammation, Th2 cells try to downregulate it.

A striking pro-inflammatory Th1 and Th17 cytokine response like IFN-γ, TNF-α, IL-15 and IL-17 during the acute phase of MERS- CoV infection in humans induced a strong inflammatory response worsening the disease[66]. Cytokine storm involving elevated levels of pro-inflammatory IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, G-CSF, GMCSF, IFN-γ, TNF-α, IP10, MCP1, MIP1α and MIP1β cytokines and chemokines in COVID-19 patients leads to pulmonary edema and damage to lung, liver, heart, and kidney[8,67].

Th17 type pro-inflammatory cytokine storm has been consistently observed in MERS-CoV and SARS-CoV patients[68,69] along with experimental model of pandemic H1N1 influenza virus associated with acute injury and poor prognosis[68,70]. SARS-CoV2 infection also induces generation of an important pro-inflammatory IL-6 cytokine, worsening COVID-19 symptoms[71-73].

Systemic inflammatory response syndrome (SIRS) or SIRS-like immune disorders causing multiple organs failure (MOF) are at the centre stage of high mortality associated with MERS, SARS and SARS-COV2[74,75]. The over activation of the immune system known as "cytokine storm" in critical cases of COVID-19 infection may have led to severe inflammatory state exacerbating the ischemia or stroke[76].

Further, SARS-COV2 not only infects macrophages, microglia, and astrocytes in the CNS but also activate glial cells leading to a chronic inflammatory state and brain damage[77].

RBC Lysis

A recently developed nomogram indicates that older age, high serum lactate dehydrogenase, C-reactive protein, the coefficient of variation of red blood cell distribution width (RDW), blood urea nitrogen, direct bilirubin and low albumin are associated with severe COVID-19. Amongst them, RDW is an important predictor of disease severity suggesting the critical role of RBCs in the worsening of COVID-19[78]. Early studies have shown RDW as reliable predictor of interstitial pneumonia worsening, ARDS[79,80], bloodstream infection and mortality in critically ill[81].

Pro-inflammatory interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) cytokine might be the reason of high variation in RBC size and decreased deformability in COVID-19 patients. Additionally, IL1, TNF-α along with IFN-γ may also decrease the erythropoiesis by reducing renal erythropoietin (EPO) production. They may also induce apoptotic death in erythroid progenitors and decrease the EPO receptor expression[82].

It is highly likely that less deformability of RBC is caused by the sepsis triggered by COVID19 leading to an increased systemic oxidative injury and damaged organ systems. The systemic inflammation may also cause microcirculation dysfunction[83], vascular reactivity[84], platelet aggregation, and white blood cell adhesion to the endothelium[83]. The persistent inflammatory status may lead to lipid peroxidation of the RBC membrane, alteration of RBC membrane pumps, an influx of calcium into the RBC and changes in 2,3-diphosphoglycerate levels[85].

RBC lysis releases intracellular content including cytokines in circulation including many inflammatory in nature contributing to the disease[86]. Recent reports suggest occurrence of RBC lysis in COVID19 patients reflected by high heme ions and ferritin level which is also associated with poor prognosis. One of the flip sides of RBC lysis is the release of cell free hemoglobin (CFH), an established mediator of disease and a poor prognostic marker in sepsis and ARDS leading to multiple organ damage. Low levels of haptoglobin, hemopexin, and heme oxygenase-1 critically hamper CFH detoxification[87,88]. Persistently high CFH levels lead to oxidation of ferrous hemoglobin to ferric and the ferryl hemoglobin radical[89] along with peroxidation of membrane lipids and an eventual multiple organ failure[90].

The RBC lysis after SARS CoV2 infection presumably involves these hematological factors in COVID-19. Recent reports show that autoimmune hemolytic anemia (AIHA)[91,92] and Acute Hemolytic Anemia (AHA) are associated with COVID-19[93-95]. Autoimmune thrombocytopenic purpura and coagulopathy are the other hematological complications reported in COVID-19 patients[91,96,97].

The precise pathophysiology of AIHA remains to be elucidated; however, the use of non- validated hydroxychloroquine has caused serious hemolysis in glucose- 6- phosphate dehydrogenase deficient COVID-19 patients[98].

Therapeutic Interventions Targeting CFH

Early results have shown decreased inflammation and alveolar fluid accumulation in diseases like malaria and sepsis by scavenging CFH by using haptoglobin, hemopexin, and heme oxygenase-1[99]. Another therapeutic candidate is acetaminophen that can inhibit the peroxidase activity of oxidized hemoglobin by reducing the ferryl (4+) hemoglobin radical to the ferric (3+) state and thus may prevent oxidative injury[100] (Figure 2).

Adjuvant Therapies Targeting Oxidative Stress in COVID-19

Oxidative stress, resulting from the disparity between the oxidizing system (like free radicals, reactive oxygen species, ROS)[101] and antioxidant systems occurs in many viral infections and can also be triggered by SARS- Co-V2[102,103]. The mitochondrial dysfunction after the viral entry into the cell along with cytokine storm is likely the sources of ROS leading to hyperinflammation, cytopenia and hyperferritinemia in COVID-19[17]. Generally free radicals can be neutralized using glutathione, an antioxidant which blocks viral replication too[104]. Certain trace elements like Zinc and Selenium, vitamin D, E and C, carotenoids and polyphenols can also help in reducing the oxidative stress[101,103,105].

N Acetyl cysteine (NAC) has been found to increase the synthesis of glutathione and glutathione-S-transferase activity in case of sepsis[106]. Additionally, NAC can also down regulate the production of IL-8, IL-6, ICAM and activation of NF- kB in sepsis and ARDS conditions in COVID-19[107,108]. Early studies showed that vitamin C and E reduce oxidative stress by blocking the NAPH oxidase, the activation of protein phosphatase 2A and TNF- α[109-112]. The adjuvant uses of vitamin E and vitamin C in COVID-19 may decrease ARDS incidence.

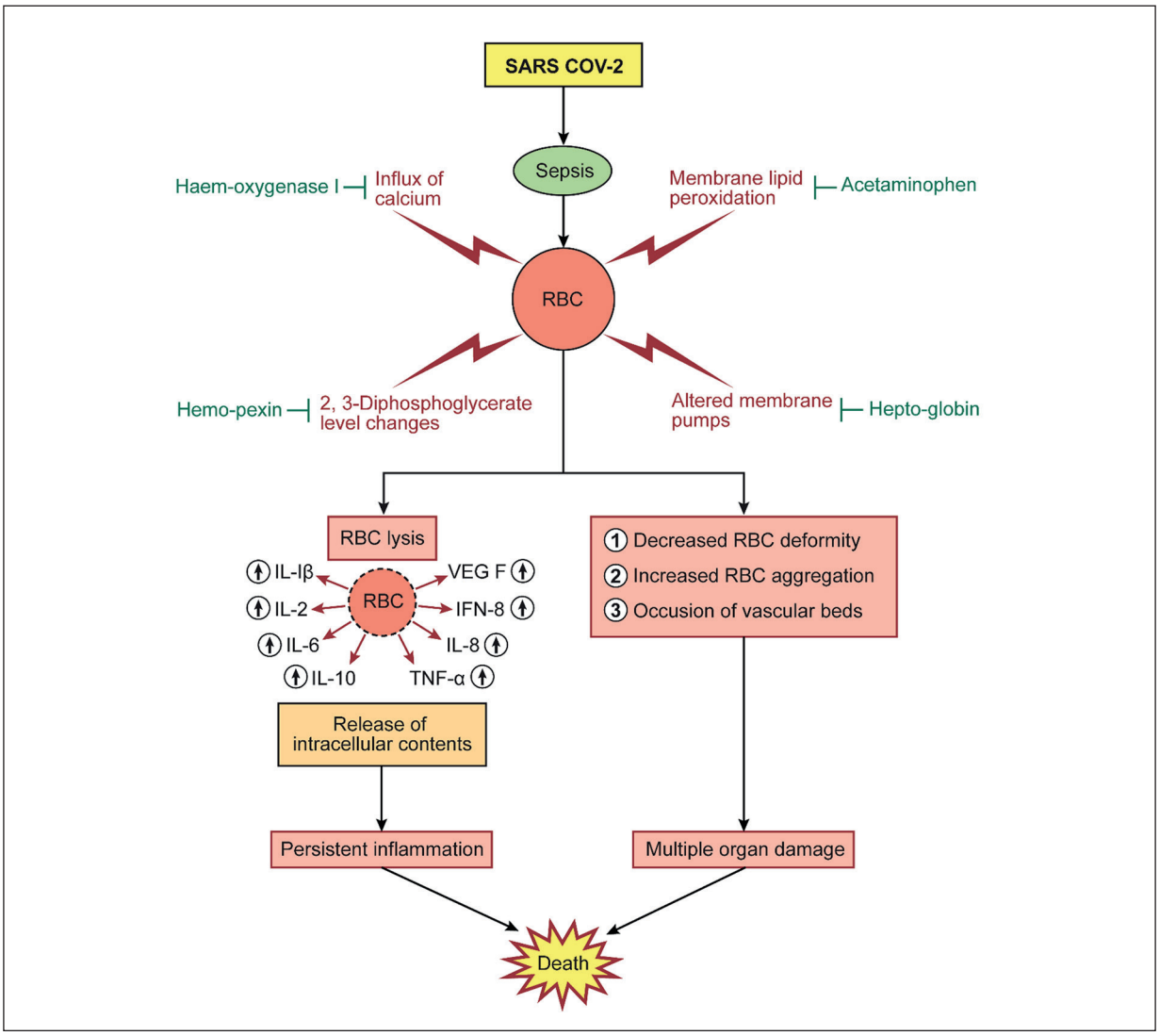

Figure 2. Pathogenesis of COVID-19 and potential use of haptoglobin, hemopexin, heme oxygenase-1 and acetaminophen. SARS-CoV-2 infection likely induces sepsis resulting in increased inflammation, oxidative stress, cytokine storm and an eventual multiple organ damage through RBC lysis. Haptoglobin, hemopexin, heme oxygenase-1 and acetaminophen may prevent RBC lysis and in turn organ damage.

Like NAC, and melatonin (MT) increases the intracellular glutathione synthesis[113] and restores mitochondrial function in organelles under oxidative stress by reducing the levels of hydrogen peroxide[114]. MT may also reduce the sustained inflammatory conditions apart from modulating the immune response in COVID-19.

Quercetin (QRC) inhibits the H+ -ATPase of the lysosomal membrane and the ATPase of proteins leading to increased bioavailability of drugs[115-117]. QRC may also reduce oxidative stress and inflammatory conditions in COVID-19.

Early evidence shows that pentoxifylline maintains mitochondrial viability by increasing the glutathione levels[118]. It further decreases the levels of CRP and blocks TNF- α production[119,120] which may reduce inflammation associated with ARDS.

Future Perspectives

Latest reports indicate the use of antiplatelet drugs and low molecular weight heparin apart from other stroke therapies to manage severe strokes associated with COVID-19. However, fur-

ther randomized trials are needed to determine the efficacy and safety of high dose corticosteroids and IVIG use in viraemic/ lymphopenic and ADEM/ GBS conditions, respectively. Detailed clinical, laboratory, biomarker and pathological studies are also warranted to elucidate the etiology of COVID-19 mediated vascular complications.

Conclusions

COVID-19, both mild or severe, is causing neurological complications like ADEM, brain inflammation, stroke and nerve damage across genders, ethnicities, in patients with or without comorbidities. These complications are likely originating from direct SARS- Co-V2 damage, pro-inflammatory cytokine storm setting a persistent inflammatory state and vasculopathy influencing changes in blood vessels. Sepsis, hypoxia, changes in coagulability and autoantibody production to neuronal antigens are also contributing to disease progression. An improved understanding of the strokes, seizure like symptoms which can be the early manifestations of abnormal brain swelling, inflammation, neurodegeneration and nerve cell death is of the greatest importance for better clinical management of COVID-19 patients. Furthermore, adjuvant antioxidant therapy may reduce oxidative damage.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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