Hypothesis

COVID-19, Mast Cells, Cytokine Storm, Psychological Stress, and Neuroinflammation

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Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new pandemic infectious disease that originated in China. COVID-19 is a global public health emergency of international concern. COVID-19 causes mild to severe illness with high morbidity and mortality, especially in preexisting risk groups. Therapeutic options are now limited to COVID-19. The hallmark of COVID-19 pathogenesis is the cytokine storm with elevated levels of interleukin-6 (IL-6), IL-1β, tumor necrosis factor-alpha (TNF-α), chemokine (C-C-motif) ligand 2 (CCL2), and granulocyte-macrophage colony-stimulating factor (GM-CSF). COVID-19 can cause severe pneumonia, and neurological disorders, including stroke, the damage to the neurovascular unit, blood-brain barrier disruption, high intracranial proinflammatory cytokines, and endothelial cell damage in the brain. Mast cells are innate immune cells and also implicated in adaptive immune response, systemic inflammatory diseases, neuroinflammatory diseases, traumatic brain injury and stroke, and stress disorders. SARS-CoV-2 can activate monocytes/macrophages, dendritic cells, T cells, mast cells, neutrophils, and induce cytokine storm in the lung. COVID-19 can activate mast cells, neurons, glial cells, and endothelial cells. SARS-CoV-2 infection can cause psychological stress and neuroinflammation. In conclusion, COVID-19 can induce mast cell activation, psychological stress, cytokine storm, and neuroinflammation.

Keywords

angiotensin-converting enzyme 2, COVID-19, cytokine storm, mast cells, neuroinflammation, severe acute respiratory syndrome coronavirus 2, traumatic brain injury

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes Coronavirus Disease 2019 (COVID-19). It is a new, rapidly spreading, and highly contagious pandemic infectious disease that was first identified in Wuhan, China (Sohrabi and others 2020). Currently, COVID-19 affected 216 countries with a total confirmed cases of 11.8 million, and 0.54 million deaths worldwide (as of July 8, 2020; World Health Organization, Geneva, Switzerland). A total number of positive case and overall deaths were 2.9 million and 0.13 million, respectively, in the United States (as of July 8, 2020; Center for Disease Control and Prevention [CDC], Atlanta, GA). The lack of prior immunity to SARS-CoV-19 caused this very high rate of infection globally.

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COVID-19 caused the loss of jobs, loss of income, psychological and other stress-associated mental impairment and suicides, and economic losses. COVID-19 also affected industries, education, health care, research, and infrastructural systems globally (Manjili and others 2020). A recent study with 1015 participants indicates that Americans experience high COVID-19-associated stress and need mental health intervention (Park and others 2020). The SARS-CoV-2 infection could be asymptomatic or can cause COVID-19 (Ciotti and others 2019; Debuc and Smadja 2020; McKee and others 2020). COVID-19 causes mild (about 80%) to severe illness with high morbidity and mortality, especially in older people, subjects with underlying health problems such as diabetes, cardiovascular disease, cancers, asthma, and severe pneumonia that requires a mechanical ventilator (Singh and others 2020; Tay and others 2020; Zhang and others 2020a; Zheng and others 2020). COVID-19 affects all ages, including children that causes inflammatory cytokine-associated Kawasaki disease like illness (Ronconi and others 2020). SARS-CoV-2-specific therapeutic options are limited or currently in development and testing phases for COVID-19 (Crisci and others 2020; Felsenstein and others 2020; Li and others 2020b; McCreary and Pogue 2020; Zhang and others 2020a). The severity of the disease lies in the ability of immune cells to stem viral and other infections.

The present hallmark of COVID-19 pathogenesis is the "cytokine storm" that causes elevated levels of proinflammatory cytokines and chemokines such as interleukin-6 (IL-6), IL-1β, tumor necrosis factor-alpha (TNF-α), chemokine (C-C-motif) ligand 2 (CCL2), and granulocyte-colony stimulating factor (G-CSF; Azkur and others 2020; Debuc and Smadja 2020; Li and others 2020d; Nile and others 2020; Wilson and Jack 2020). Symptoms such as "fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, the new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea" may develop in COVID-19 patients after 2 to 14 days of exposure (CDC, Atlanta, GA). COVID-19 can cause systemic as well as many neurological disorders such as headaches, fever, dizziness, cerebrovascular disease, hypogeusia, hyposomia, neuralgia, stroke, epilepsy, impaired consciousness, encephalopathy, and psychiatric disorders (Dixon and others 2020; Finsterer and Stollberger 2020; Khalili and others 2020; Li and others 2020a; Ogier and others 2020; Wilson and Jack 2020), as shown in Table 1. COVID-19 is a risk factor for stroke (Markus and Brainin 2020). COVID-19 symptoms may develop 2 to 14 days after the initial exposure to the SARS-CoV-2 (CDC, Atlanta, GA). The central nervous system (CNS) dysfunction in COVID-19 increases the poor outcome of the patients. Though the research on COVID-19 is very active globally, the pathogenesis is not yet clearly understood. Previous studies have shown that peripheral immune response and inflammation can cause and exacerbate acute and chronic neuroinflammatory response (Cabrera-Pastor and others 2019; Kempuraj and others 2017; Kempuraj and others 2019a; Kempuraj and others 2019b; Kustrimovic and others 2019; Magrone and others 2020; Skaper and others 2017; Stuve and Zettl 2014). Mast cells are implicated in psychological stress, inflammatory and neuroinflammatory response (Theoharides 2020b). There are many original articles and comprehensive review articles already published on COVID-19 pathogenesis. However, there is a knowledge gap in understanding the COVID-19 infection and the neuroinflammatory responses in the brain, especially concerning psychological stress, mast cell activation, and cytokine storm–associated responses. In this present hypothesis article, we discuss the possible link between COVID-19, mast cell activation, psychological stress, cytokine storm, and exacerbation of neuroinflammatory responses. The data for this hypothesis manuscript have been collected from the PubMed website. We want to point out that as the understanding and the knowledge about the COVID-19 pathogenesis is continuously and rapidly expanding, the view and the data presented here may change in the future.

SARS-CoV-2-Associated Mast Cell Activation, Cytokine Storm, Psychological Stress, and Upregulation of Neuroinflammatory Responses

Mast Cell Activation

Mast cells are innate immune cells that also participate in adaptive immune mechanisms. Mast cells are implicated in viral infections, systemic inflammatory diseases, asthma, neuroinflammatory diseases, traumatic brain injury (TBI)/stroke, and several stress disorders. Mast cells are ubiquitous in the body, primarily concentrated in the lung, airways/respiratory tract, gastrointestinal tract, skin, nasal passage, and meninges, where they fight against invasion of infective microorganisms such as viruses and bacteria, and toxins (Arac and others 2019; Kempuraj and others 2017). Mast cells are highly heterogeneous and differ in ultrastructure, morphology, mediator content, receptor expression, and responses to various stimuli. This makes mast cells to function differentially to different stimuli, both protective role and deleterious effects in the body, and different functions in the different tissues microenvironment (Mukai and others 2018; Skaper and others 2013; Varricchi and others 2019). Mast cells are implicated in protective response as well as a deleterious response based upon the nature, duration, and

Table 1. COVID-19-Associated Neurological Dysfunctions.

No.	Neurologic and Other Important Disorders in COVID-19
1	*Central Nervous System*
	Headache, dizziness, impaired consciousness, cognitive impairments, mental disorder, acute cerebrovascular disease, epilepsy, ischemic stroke, psychological stress, hypercytokinemia, encephalopathy, and neuroinflammation
	Peripheral Nervous System
	Visual impairment, anosmia (decreased smell sensitivity), hypogeusia (decreased taste sensitivity), and neuralgia
	Skeletal muscle injury—muscle pain and fatigue
2	*Respiratory System*
	Lung injury, pneumonia, severe acute respiratory syndrome (SARS)-acute respiratory distress syndrome (ARDS)
3	*Immunity, Cytokine Storm (excessive systemic inflammatory response) and other toxic inflammatory mediators*
	Innate immune hyperactivity, adaptive immune dysregulation, innate immune-mediated cytokine storm IL-6, IL-1β, TNF-α, CCL2, GM-CSF, CXCL10, IL-12, IFN-γ
	Mast Cells
	Histamine, tryptase, chymase, LTC4, PDG2, as well as IL-6, IL-1β, TNF-α, CCL2, GM-CSF, CXCL10, IL-12, VEGF, IFN-γ
	Macrophage activation, lymphopenia, reduced T cells, reduced $CD4^+$ T cells and $CD8^+$ T cells, increased Th17 cells, eosinopenia, agammaglobulinemia, high D-dimer and C-reactive protein (CRP), and lactate dehydrogenase
4	*Other General Signs and Symptoms*
	Fever or chills, dry cough, fatigue, sputum production, shortness of breath or difficulty breathing, sore throat, nausea or vomiting, nasal congestion or runny nose, diarrhea, myalgia/arthralgia, dyspnea, anosmia, abdominal pain, and cardiac dysfunctions
5	*Disease progression*
	a. Asymptomatic—incubation period (2-14 days)
	b. Mild to moderate symptoms (about 81%)—fever, cough
	c. Severe disease symptoms with hyper inflammation stage (about 14%)—acute respiratory distress syndrome, sepsis, organ failure
	d. Critical condition (about 5%)—recovery or death

IL-6 = interlukin-6; IL-1β = interleukin 1beta; CRP = C-reactive protein; IFN-γ = interferon-gamma; LTC4 = leukotriene C4; TNF-α = tumor necrosis factor-alpha; CCL2 = chemokine (C-C-motif) ligand 2; GM-CSF = granulocyte macrophage-colony stimulating factor; PGD2 = prostaglandin D2; CXCL10 = chemokine (C-X-C motif) ligand 10.

site of activation in the body. Mast cells play a significant role in the first line of defense against viruses and bacteria that are entering into the body. Recent reports indicate that coronavirus activates innate immune cells such as monocytes/macrophages, neutrophils, T cells, natural killer (NK) cells, mast cells, resident tissue epithelial and endothelial cells, and induce cytokine storm in the lung (Azkur and others 2020; Kritas and others 2020; Sun and others 2020; Theoharides 2020a; Ye and others 2020). Coronavirus entry into the body is primarily attacked by innate immune cells, including mast cells, which are commonly present in the nasal passage and lower respiratory tract in COVID-19 (Kritas and others 2020). SARS-CoV-2 can activate mast cells present in the respiratory tract in the initial stage of the disease. The severity of the disease lies in the ability of innate immune cells to stem viral and other infections.

Mast cells release proteases, histamine, and many pro-inflammatory cytokines and chemokines, and exacerbate allergic, asthma, and inflammatory reactions (Kempuraj and others 2016; Kempuraj and others 2017; Kempuraj and others 2019a; Theoharides and others 2012). Mast cell activation in response to viral infection may lead to protective function by directly fighting infection or helping the immune system. However, extensive mast cell activation leads to increased levels of inflammatory cytokine and chemokine release that further worsen inflammation and increase disease severity. The virus activates mast cells to release several proinflammatory molecules, including histamine, tryptase, IL-1β, CCL2, IL-6, GM-CSF, and TNF-α, which are implicated in COVID-19 disease. Mast cell cytoplasm contains about 50 to 200 granules that store histamine, proteases, heparin, chondroitin sulfate, and proinflammatory and anti-inflammatory cytokines/chemokines that are released after activation (Elieh Ali Komi and others 2020; Gilfillan and others 2011). Mast cells can immediately release prestored TNF-α, histamine, and proteases from the cytoplasmic granules by degranulation, and later newly synthesized TNF-α and other cytokines and chemokines in the late phase of reactions (Karamloo and Konig 2020; Kritas and others 2020; Theoharides 2020a). Mast cell-released protease tryptase can promote the infection by SARS-CoV-2 (Theoharides 2020a). Viruses can activate mast cells through Toll-like receptors (TLRs) and increase inflammatory mediator expression. Moreover, mast cells

can detect damage-associated molecular patterns (DAMPs) from various types of viruses, and thus, mast cells can detect and respond to SARS-CoV-2 infection. Innate immune cells may be activated by DAMPs and pathogen-associated molecular patterns (PAMPs) in COVID-19 (Vardhana and Wolchok 2020). Recent reports suggest that COVID-19 can activate mast cells through TLRs and contribute to pulmonary inflammation and fibrosis (Gigante and others 2020; Karamloo and Konig 2020; Kritas and others 2020; Theoharides 2020a).

The binding of SARS-CoV-2 with its spike (S) protein to angiotensin-converting enzyme 2 (ACE2) is at least 10 times stronger than that of other SARS viruses, which may be an essential factor influencing higher COVID-19 infection rates in humans. ACE2 is ubiquitous and is highly expressed on type II alveolar epithelial cells, tracheal and bronchial epithelial cells, macrophages, type 2 pneumocytes, and endothelial cells in the lung (Li and others 2020f; Li and others 2020c; Vinciguerra and Greco 2020; Xia and Lazartigues 2008). Wide surface expression of ACE2 in the lung makes it highly vulnerable to SARS-CoV-2 infection (Verdecchia and others 2020). ACE2 is expressed in the heart, vessels, gut, kidney, and brain (Verdecchia and others 2020). ACE2 mobilizes hematopoietic cells and other cells to the vascular damage/ischemic area for revascularization during the tissue repair process (Debuc and Smadja 2020). Neuronal ACE2 receptors are primarily found in brainstem cells that regulate respiratory and cardiac functions. Thus, SARS-CoV-2 infection in these pathways may play an essential role in acute respiratory distress syndrome (ARDS), and cardiac complications that contribute to COVID-19 mortality (Cure and Cumhur Cure 2020; Long and others 2020; Mankad and others 2020; Saleki and others 2020). SARS-CoV-2 infection is associated with viral entry into the cells that decrease ACE 2 levels and increase inflammatory responses (Verdecchia and others 2020). ACE2 is used for entry, and transmembrane protease serine subfamily member 2 (TMPRSS2) for S protein priming. Mast cell activation contributes to neuroinflammation, and neurodegeneration in many neurodegenerative diseases, including TBI and stroke pathogenesis (Arac and others 2019; Jones and others 2019; Kempuraj and others 2017; Kempuraj and others 2019a).

Immune Response and Cytokine Storm

SARS-CoV-2 infection induces immediate and late host immune responses. The innate immune response is the first line of defense after infection; adaptive immune responses also clear viral and other infections immediately and in subsequent infections. T cells can directly attack and destroy viruses. Antigen-presenting cells such as monocytes/macrophages, dendritic cells, neutrophils, B cells, and mast cells transfer antigens to memory T cells and B cells. On the other hand, B cells produce antibodies against the viruses that, in turn, destroy viruses in the subsequent attacks. However, the precise mechanism of antigen presentation, innate, cellular and humoral immune responses, and cytokine storm to SARS-CoV-2 infection are not yet clearly understood. Lymphopenia is the decreased lymphocyte count, is associated with decreased total T cells, $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and increased proinflammatory Th17 cells, and perforin are reported in COVID-19 patients (Hotez and others 2020; Pedersen and Ho 2020). Increased level of IL-6 in COVID-19 patients can induce the differentiation of Th17 cells and upregulate cytokine storm, and lung inflammation and dysfunction (Hotez and others 2020; Wu and Yang 2020). Recovery of lymphocyte counts toward normal levels indicates the clinical improvement of COVID-19 patients (Vardhana and Wolchok 2020).

The level of cytokine storm and lymphopenia are considered as biomarkers for COVID-19, and these levels are currently used to predict the severity of the disease and the mortality in these patients (Debuc and Smadja 2020). COVID-19 is also associated with increased pro-coagulation factors such as fibrinogen, prolongation of prothrombin time, and D-dimer that contribute to pulmonary embolism and increased mortality of these patients (Connell and others 2020; Pineton de Chambrun and others 2020). COVID-19 patients show increased D-dimer level and suggested this could be used to predict mortality/prognosis (Connors and Levy 2020; Li and others 2020e; Qiu and others 2020; Zhang and others 2020b). Coagulation disorders associated with increased cerebral bleeding increase the risk of stroke, neuroinflammation, and cognitive decline. Coagulation disorder cause, clot formation, and bleeding tendency that increase the risk of stroke, neuroinflammation, and cognitive decline in COVID-19 patients. Severe COVID-19 infection can cause significantly high levels of inflammatory cytokine production, ischemic stroke, cerebral vascular damage, clinical deterioration, and increased mortality rate (Khalili and others 2020). Studies report stroke is associated with coagulopathy, antiphospholipid antibodies, and multiple infarcts in COVID-19 patients (Pineton de Chambrun and others 2020; Zhang and others 2020c). The presence of coronavirus has been shown in the brain and cerebrospinal fluid (CSF). In vitro study indicates that SARS-CoV-2 can replicate in the neuronal cells (Rogers and others 2020). SARS-CoV-2 can spread from one neuron to another through axonal transport. Recent reports suggest that SARS-CoV-2 can enter the brain through the damaged blood-brain barrier (BBB), olfactory bulb/olfactory nerve, or lymphatic drainage (Finsterer and Stollberger 2020; Li and others 2020a; Fig. 1). SARS CoV-2 can infect and directly cause endothelial cell damage, increase BBB

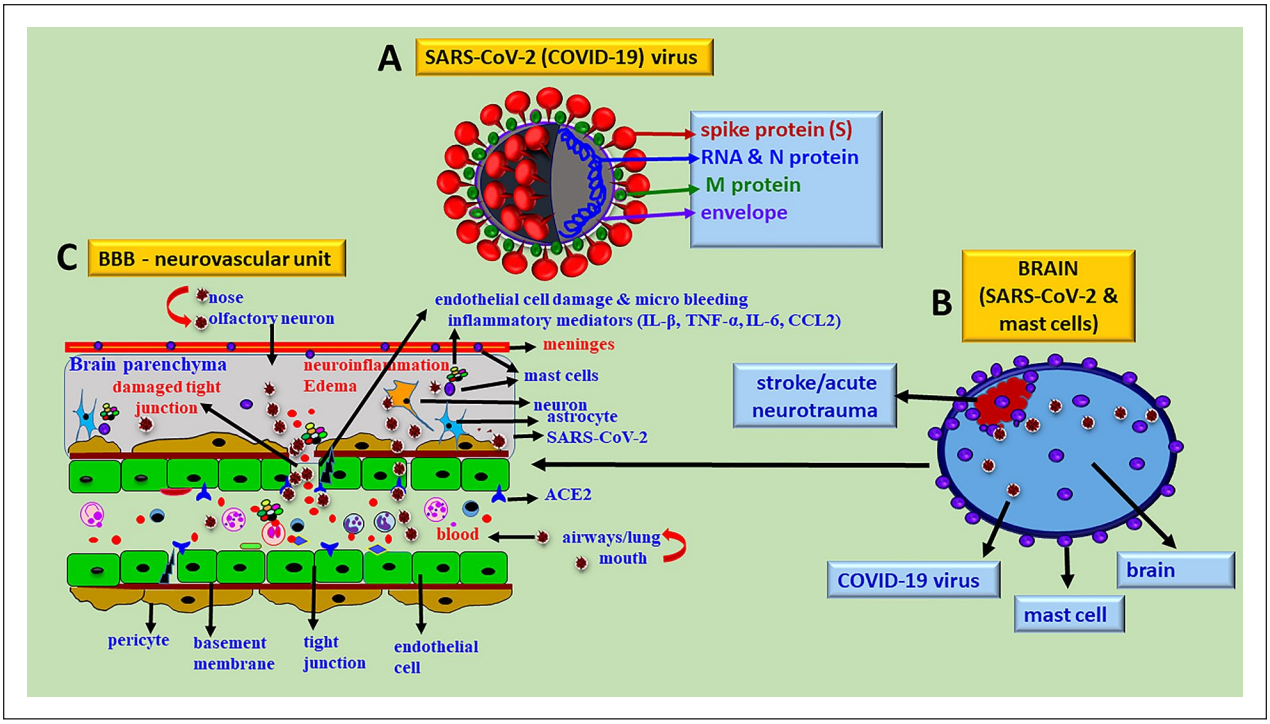

Figure 1. Schematic diagram showing how COVID-19 can cause and exacerbate neuroinflammatory response in the brain. (A) SARS-CoV-2, (b) brain infected with SARS-CoV-2, and (C) neurovascular unit, damaged BBB/loss of tight junction, and neuroinflammation in brain parenchyma. Mast cells, glial cells, endothelial cells, and neurons can be activated by SARS-CoV-2 in the brain. SARS-CoV-2 can enter the brain through the nose, olfactory nerve, defective BBB, and lymphatic drainage. SARS-Cov-2 can activate mast cells and glial cells in the brain to release inflammatory mediators. Endothelial cells in the brain express SARS-CoV-2 receptor ACE2 through which SARS-CoV-2 can infect and activate. Inflammatory mediators released from brain cells and periphery could cause BBB breach, tight junction damage, edema, micro bleeding, cognitive decline, stroke, and neuroinflammation. ACE2 = angiotensin-converting enzyme 2; BBB = blood-brain barrier; COVID-19 –= coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

permeability, and cause edema formation. It has been reported that ACE2 is expressed in the CNS in physiological conditions in neurons and glial cells, making the brain more vulnerable to COVID-19 infection (Baig and others 2020; Finsterer and Stollberger 2020). Viral infection and replication also induce cell death. Neurological disorders may contribute to the morbidity and mortality of COVID-19 patients. Spike protein (S1) of the coronavirus binds to the ACE2 of neurons (Li and others 2020a). S protein consists of S1 (for attachment) and S2 (for membrane fusion) subunits (Ou and others 2020). The SARS-CoV-2's proteins that are responsible for the entry and replication of the virus are membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins (Gasparyan and others 2020). The infected neurons can release inflammatory molecules that can activate nearby immune cells, including mast cells, endothelial cells, pericytes, neurons, microglia, and astrocytes. As cerebral endothelial cells express ACE2, SARS-CoV-2 infection can cause intracerebral bleeding, and BBB dysfunctions (Finsterer and Stollberger 2020; Li and others 2020a). This can cause endothelial cell damage, cerebral edema formation, neuronal death, and cognitive decline.

Death due to severe COVID-19 is based on gender, age, underlying disease comorbidity, and importantly the magnitude of innate and adaptive immune responses (Manjili and others 2020). SARS-CoV-2 or virally activated mast cells can immediately release histamine, prostaglandin D2 (PGD2), and leukotriene C4 (LTC4), and induce acute bronchoconstriction and lung inflammation (Kritas and others 2020). Mast cells are very critical in allergy, asthma, lung diseases, and more recently, in COVID-19 pathogenesis (Theoharides 2020a). A recent report indicates that COVID-19 exacerbates asthma severity, as mast cells are critical in asthma pathogenesis (Ritchie and Singanayagam 2020). Thus, asthma and COVID-19 comorbidity may exacerbate the disease severity. Mast cell degranulation–derived serine-protease tryptase and other mast cell–mediated inflammatory mediators are implicated in SARS-CoV-2 infection (Theoharides 2020a). Activated mast cells release histamine, LTC4, and PGD2 that induce bronchoconstriction,

increased mucous production, and cough. Mast cell activation and degranulation in the respiratory tract increases vascular permeability, cause localized edema, congestion, and fluid accumulation (Krystel-Whittemore and others 2015). These reports indicate that mast cell activation in the respiratory tract can contribute and exacerbate lung inflammation, and lung failure in COVID-19.

Dysregulated and insufficient innate immune protective responses play a significant role in the onset, progression, and severity of COVID-19. In severe COVID-19 cases, cytokine storm is the primary cause of the increased mortality, multi-organ failure, ARDS, and intravascular coagulation (Azkur and others 2020). However, the mechanism of cytokine storm is very complex and not yet clearly known in COVID-19 (Ye and others 2020). Most of the COVID-19 patients show mild to moderate disease in the first week. Later on, some patients show extensive pneumonia, cytokine storm, ARDS, multi-organ dysfunction, and ultimately organ failure, and disseminated intravascular coagulation in about 3 weeks after the disease onset (Azkur and others 2020). ARDS, followed by multi-organ failure, is the central immunopathological disorder due to cytokine storm in COVID-19 patients (Li others 2020d; Moore and June 2020). Cytokine storm is a deadly systemic hyperinflammatory response. It involves activation of macrophages, leukocytes, mast cells, endothelial cells in an autocrine and paracrine effect associated with large amounts of proinflammatory cytokines and chemokines release in COVID-19 (Azkur and others 2020; Li others 2020d). These immune mediators released include IL-6, IL-8, IL-1β, TNF-α, CCL2, CCL5, IL-17, IL-18, IL-33, CXCL-10, interferon-γ (IFN-γ), IL-12, and GM-CSF from immune effector cells (Azkur and others 2020; Table 1). SARS-Cov-2 infection can activate mast cells in the respiratory tract and can contribute to the cytokine storm. Activated monocytes, macrophages, and dendritic cells release IL-6 in COVID-19 patients (Moore and June 2020). Inflammatory mediators released from SARS-CoV-2 activated immune cells, including mast cells, can significantly contribute to the cytokine storm and respiratory dysfunction in COVID-19. Uncontrolled excessive production of inflammatory mediators and sustained systemic inflammatory response causes ARDS, multiple organ failure, and death of COVID-19 patients (Li and others 2020d). Cytokine storm-induced lymphopenia prevents the production of antiviral antibodies by the adaptive immune system that is necessary for the clearance of viruses (Manjili and others 2020). An elevated level of IL-6 correlates well with the need for ventilation and mortality (Vardhana and Wolchok 2020). Tocilizumab is an anti-IL-6 monoclonal antibody that is currently used to treat cytokine storm in COVID-19 patients-associated with an elevated level of IL-6 in the blood (Barlow and others 2020; Cao 2020; Xu and others 2020). Leukotrienes and reactive oxygen species (ROS) released from neutrophils induce lung injury by damaging endothelial cells and pneumocytes (Vardhana and Wolchok 2020). Though all COVID-19 patients develop cytokine storm, high-risk individuals with diabetes, obesity, hypertension, smoking, and lung disease develop a severe form of cytokine storm in COVID-19 (Gasparyan and others 2020). Alveolar macrophages with ACE2 are the high targets of SARS-CoV-2. An essential feature of the acute stage of COVID-19 is that there is a simultaneous increase in serum IL-6 associated with impairment of other innate immune functions, including neutrophils (Blanco-Melo and others 2020). Recent reports indicate that SARS-CoV-2 affects women less than men (Mehra and others 2020). Women generally produce higher levels of antibodies that remain in circulation for a more extended period. Additionally, the production of IL-6 after the viral infection is lower in women than in males (Conti and Younes 2020). Gender differences in innate and adaptive immunity also cause gender-related susceptibility for COVID-19 (Manjili and others 2020). Generally, in response to pathogens, women resolve acute inflammation and suppress inflammatory response better than men in increased production of lipoxins, protectins, resolvins, and maresins (Manjili and others 2020). It has been reported that the correlation between ACE2 expression and immune responses is different between females and males as well as young and old in the lung that makes a difference in disease severity (Li and others 2020c).

Psychological Stress Due to COVID-19

Social distancing, quarantine, fear, loneliness, loss of family members or friends, loss of job, and financial instability due to COVID-19 can cause psychological stress. COVID-19 caused significantly increased psychological stress and other stress such as restraint stress due to lockdown restrictions, and psychiatric and neuropsychiatric problems in these patients, their family members, and the general public (Park and others 2020; Rogers and others 2020; Steenblock and others 2020; Vinkers and others 2020; Wang and others 2020). Medical response professionals experience more psychological and other kinds of stressors, including being in danger, worrying about family infection, and poor sleep quality due to COVID-19 (*The Lancet* 2020; Wu and others 2020; Xiao and others 2020). A recent study in the United States reports that COVID-19-associated stress include reading/hearing about the severity and contagiousness, uncertainty about the length of quarantine and social distancing requirements, unwanted changes in daily life schedules, and financial concern is the most stressful among other stressors (Park and others 2020). Prolonged psychological stress and stressful situations such as in COVID-19

affects immunity, physical health, mental health, and increase substance abuse (Minihan and others 2020). All these factors can affect the general quality of life. Stressful situations can decrease the immune responses to infections, as well as response to vaccination in general (Minihan and others 2020). As stress and tension can increase shortness of breath in asthma and lung diseases, the stress in COVID-19 can cause more severe effects in these patients (Minihan and others 2020). Similarly, stress can cause cardiovascular/heart diseases, sleeping disorders, stomach upset, headache, and so on, in COVID-19 patients (Finsterer and Stollberger 2020; Minihan and others 2020). All these above-mentioned health disorders can contribute to significantly high levels of stress in humans. It is already known that several stress conditions can induce the onset and progression of neuroinflammatory and psychiatric disorders, including Alzheimer's disease (AD; Bisht and others 2018; Calcia and others 2016; Hasegawa 2007; Kempuraj and others 2019b; Kempuraj and others 2020; Khalsa 2015; Kim and Won 2017; Mravec and others 2017; Piirainen and others 2017). The treatment for psychological stress "Psychological First Aid" is a model used to treat patients during a disaster, such as for COVID-19 patients. Psychological stress due to COVID-19/SARS-CoV-2 infection cause the release of corticotropin-releasing hormone (CRH) and activates the hypothalamic-pituitary-adrenal axis (HPA) that leads to stress-induced depression, anxiety, psychiatric disorders, and posttraumatic stress disorder (PTSD; Li and others 2020a; Steenblock and others 2020). In fact, mast cells produce and react to CRH and many other neuropeptides that can cause and exacerbates neuroinflammation (Kempuraj and others 2019b). Mast cell–derived immune and inflammatory mediators play an important role in stress-induced disease pathogenesis, including neuroinflammatory and autoimmune diseases. Various stressful conditions worsen the clinical severity of many inflammatory disorders.

Stress is the second most frequent inducer of headaches due to inflammatory mediators released from mast cells in the meninges and brain. Since COVID-19 causes many neurological problems including, headache, stress, stroke, itch, cerebrovascular dysfunction, and BBB disruption, we suggest that mast cells could play a significant role in is COVID-19-induced acute and chronic disease symptoms. It has been reported that most of the COVID-19 patients with respiratory disease suffer from headaches (Acharya and others 2020; Berger 2020). Moreover, the cytokine storm in COVID-19 can increase the entry of inflammatory mediators in the brain through BBB breaches. Defective BBB could also allow the entry of SARS-CoV-2 and immune cell infiltration into the brain. All these factors can activate neurons, endothelial cells, glial cells, and cause and exacerbate acute and chronic neuroinflammatory responses. Increased inflammatory mediators and activation of glial cells contribute to the pathogenesis of neurodegenerative and neuroinflammatory diseases, including AD, Parkinson's disease (PD), Multiple sclerosis (MS), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), and neurotrauma (Heneka and others 2020; Serrano-Castro and others 2020). Recent reports indicate that cytokine storm causes intracranial cytokine storm and BBB disruption in COVID-19, indicating this disease can influence and exacerbate neuroinflammatory diseases, and neurotrauma pathogenesis (Coperchini and others 2020; Serrano-Castro and others 2020). The gut-brain pathway may be another route for the entry of SARS-CoV-2 into the brain (Bostanciklioglu 2020). Additionally, SARS CoV-2 can directly cause neuronal death in the brain (Serrano-Castro and others 2020). All these events can cause and exacerbate neuroinflammatory disorders. Psychological stress, anxiety, and fear can induce and increase itch sensation and exacerbate atopic dermatitis and urticarial disease severity in COVID-19 patients (Stefaniak and others 2020). Acute and chronic psychological stress can increase itch sensation through mast cell activation (Golpanian and others 2020). It is already known that mast cell–derived inflammatory mediators play an essential role in itch sensation in atopic dermatitis and urticaria, indicating mast cell involvement in COVID-19 pathogenesis.

Activated glial cells and immune cells, including mast cells in the brain, release inflammatory cytokines and chemokines and exacerbate neuroinflammation in neurotrauma and neurodegenerative diseases (Dong and others 2014; Kempuraj and others 2016; Kempuraj and others 2017; Kempuraj and others 2019a; Leonard and others 2020; McKittrick and others 2015; Parrella and others 2019). COVID-19 can cause neurological manifestations, long-term impact, and chronic neuroinflammation, including neurodegenerative diseases (De Felice and others 2020; Sheraton and others 2020). SARS-CoV-2 from the general circulation can enter cerebral flow where the slow movement of blood in microcirculation may facilitate attachment of SARS-CoV-2 with ACE2 of capillary endothelial cells. This can cause replication of the virus, and endothelial cell damage and the SARS-CoV-2 can enter the brain where it infects neurons and glial cells (Baig and others 2020; Natoli and others 2020; Ogier and others 2020; Saavedra 2020). TBI induces BBB disruption within hours following injury, but these effects may persist for years (Dinet and others 2019; Johnson and others 2018; Kempuraj and others 2019a). TBI causes loss of tight junction proteins that leads to edema, neuroinflammation, neurodegeneration, and cognitive decline (Blixt and others 2015; Kempuraj and others 2019a; Logsdon and others 2015; Yeung and others 2008). Since the effect of TBI can

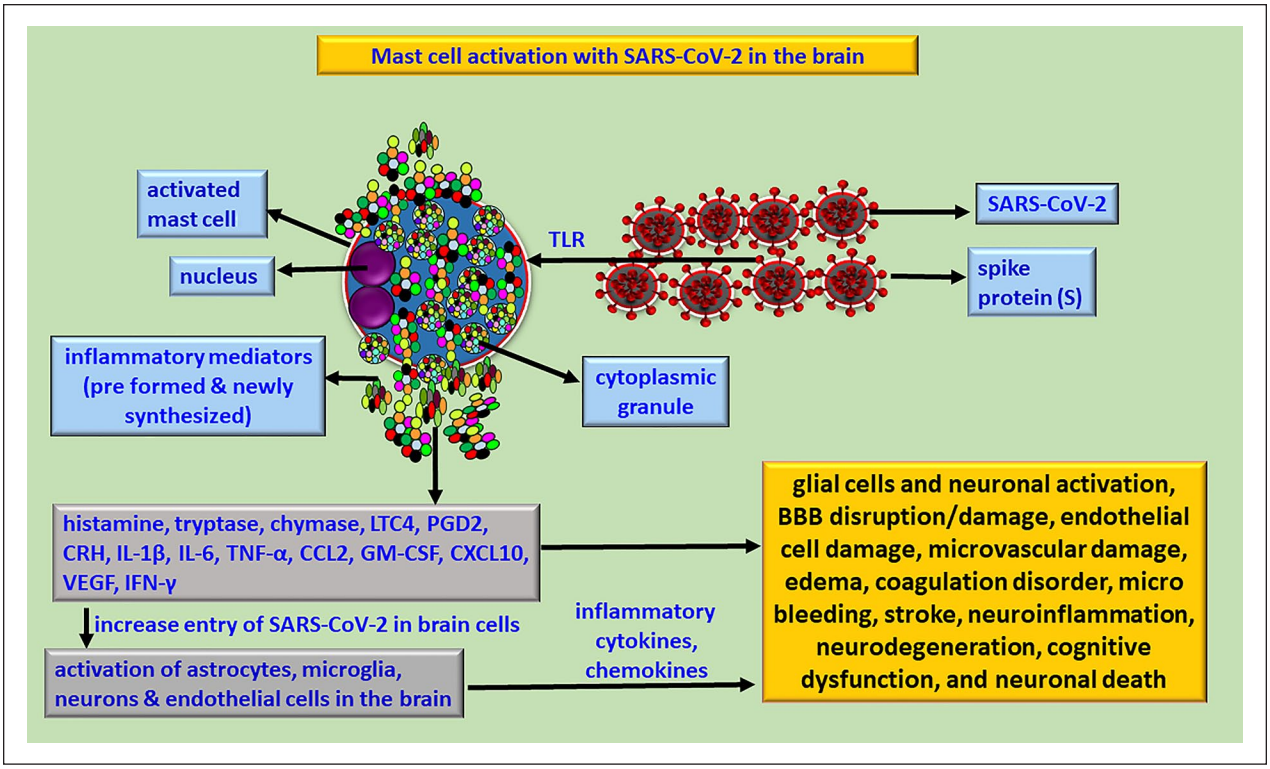

Figure 2. Schematic diagram showing a mast cell activated with SARS-CoV-2 and release of various inflammatory mediators. SARS-CoV-2 can activate mast cells and release proteases tryptase and chymase that can influence COVID-19. SARS-CoV-2 can activate mast cells through TLR to release proinflammatory mediators of the cytokine storm-specific IL-6, IL-1β, TNF-α, CCL2, GM-CSF, and CXCL10 in COVID-19. These mediators cause cytokine storm that ultimately causes lung inflammation and lung dysfunction. SARS-CoV-2 infection with cytokine storm can cause BBB disruption and entry of SARS-CoV-2 in the brain. SARS-COV-2 can activate brain cells and mast cells to release additional inflammatory mediators. These inflammatory mediators can cause additional glial cells and neuronal activation, and cause headaches, BBB disruption, neuroinflammation, neurodegeneration, and cognitive decline in COVID-19. Activation of mast cells in the meninges causes headaches in any stressful conditions, including in COVID-19. ACE2 = angiotensin-converting enzyme 2; BBB = blood-brain barrier; COVID-19 = coronavirus disease 2019; CRH = corticotropin-releasing hormone; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLRs = toll-like receptors.

persist for many years, SARS-CoV-2/COVID-19 comorbidity, and chronic stress can increase TBI-induced neuroinflammatory diseases. Thus, we suggest that SARS-CoV-2 can cause and upregulate the severity of TBI/stroke pathogenesis through cerebral vascular dysfunction and micro bleeding, BBB breach, edema, activation of neurons and glial cells, neuroinflammation, neurodegeneration, cognitive decline, increased inflammatory cytokines and chemokines level, and psychiatric disorders. Moreover, acute and chronic stress due to COVID-19 also can further increase the severity of TBI pathogenesis. Since mast cells are implicated in stress as well as TBI/stroke, SARS-CoV-2 infection can upregulate the severity of these conditions through mast cell activation-associated inflammatory mediators release, including proteases, IL-6, IL-1β, TNF-α, CCL2, GM-CSF, and CXCL10 (Fig. 2).

Several international research centers and pharmaceutical companies are currently making remarkable progress toward the development of safe and effective SARS-CoV-2 vaccines and antiviral therapeutic options. Some drugs already show beneficial therapeutic effects, including suppression of the effects of cytokine storm in COVID-19 (Barlow and others 2020; Cao 2020; Chary and others 2020; Xu and others 2020). Recent clinical trials indicate some therapeutic effects of antiviral drug Remdesivir in COVID-19 patients (Barlow and others 2020). Inhibition of mast cell activation and degranulation by mast cell inhibitor drugs, anti-inflammatory drugs, antiviral drugs, and neuroprotective natural compounds such as luteolin in COVID-19 could reduce infection, inflammatory responses, pulmonary complications, and disease severity (Theoharides 2020a). Natural compounds are particularly important as these compounds can be taken regularly over a long period of time that is necessary to reduce the risk of chronic effects of due to COVID-19 comorbidity. Vitamin D supplementation can stabilize mast cells and decrease mast cell–associated inflammatory mediator release. A recent report suggest that mast cell stabilizer drugs Sodium cromoglicate and palmitoylethanolamide (PEA) can prevent the degranulation and activation, and reduce the

release of proinflammatory mediators from mast cells and can inhibit inflammation in the lung in COVID-19 patients (Gigante and others 2020). In addition to drug therapy, COVID-19 patients also need psychological treatment. The medications for COVID-19 should target and inhibit viral replication, cytokine storm, and hyperinflammatory responses to reduce acute lung injury, organ failure, neuroinflammation, and psychological stress. The use of immune nutrition and nutritional supplements with anti-inflammatory, antiviral, and antioxidant properties that boost protective immune responses may be useful to prevent or reduce the disease severity in COVID-19 patients. Additionally, it has been suggested that individuals should remain at home in quarantine for approximately 1 month to reduce viral transmission and COVID-19 aggravation (Conti and others 2020).

Conclusions and Perspective

Covid-19 can cause short-term as well as long-term effects. COVID-19 due to SARS-CoV-2 infection causes a hyper-inflammatory response associated with cytokine storm by the activation of monocytes/macrophages, dendritic cells, mast cells, T cells, and endothelial cells. SARS-CoV-2-activated mast cells can cause either protection by fighting infection or deleterious effects by inducing inflammation. COVID-19 can exacerbate neuroinflammation through psychological and other stressful conditions, activation of mast cells, neurons, astrocytes, microglia, endothelial cells, and increase inflammatory cytokine and chemokine levels in the CNS. COVID-19 is a risk factor for stroke pathogenesis. SARS-CoV-2 infection can exacerbate neuroinflammatory disorders such as neurotrauma, including TBI pathogenesis. In addition to monocytes/macrophages, dendritic cells, epithelial and endothelial cells, mast cell activation-mediated inflammatory mediators could contribute to the cytokine storm and neuroinflammatory response in COVID-19. COVID-19-associated psychological stress and other stressful conditions can cause and exacerbate acute and chronic mast cell activation that may accelerate the onset, progression, and severity of neuroinflammation and neurodegenerative diseases. The immune boosters and neuroimmune nutritional supplements in the risk groups may help reduce the risk or the severity of COVID-19. Further understanding of the immunopathological and the neuroimmunopathological mechanisms of the SARS-CoV-2 infection and COVID-19 disease pathogenesis could help for developing new therapeutic options to treat these patients.

Author Contributions

DK wrote manuscript, designed and created the figures, and critically edited the manuscript. AZ edited the manuscript, and acquired funding. GPS, MEA, SPR, RT, AK, SAZ, SSI, CB, and DJ edited the manuscript.

Declaration of Conflicting Interests

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