Journal of Neurology & Experimental Neuroscience

https://doi.org/10.17756/jnen.2020-S1-004

Commentary

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Spectrum of COVID-19: A Disorder of Multisystem Beyond Respiratory Disease

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Received: June 17, 2020
Accepted: June 22, 2020
Published: June 26, 2020

Citation: Luo JJ, Dun NJ. 2020. Spectrum of COVID-19: A Disorder of Multisystem Beyond Respiratory Disease. *J Neurol Exp Neurosci* 6(S1): S11-S20.

Published by United Scientific Group

Abstract

We are in the nascent stages of our understanding of how SARS-CoV-2 infects humans and causes COVID-19. In addition to the lungs, SARS-CoV-2 also attacks many other organs of multiple systems. Patients contracted with COVID-19, from infants to adults, may present with or without typical respiratory symptoms but symptoms of other systems including cardiovascular, gastrointestinal, urologic, hematologic, immunologic, dermatologic and central and peripheral nervous systems. Some patients may die unexpectedly. Despite limitations in our capacity to determine the mechanism underpinning COVID-19-driven pathology in the clinic, we summarize COVID-19 clinical manifestations and explore possible mechanisms underlying COVID-19 disease, including unexpected mortality.

Keywords

Coronavirus, COVID-19, Multiorgan failure, Multisystem disorder, Severe acute respiratory syndrome, SARS-CoV-2

Introduction

Coronavirus disease-2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), was considered to have originated from a zoonotic disease [1, 2] that has already spread globally and infected several millions of humans. SARS-CoV-2 is highly contagious and COVID-19 has a high mortality rate in severe patients. Symptoms of COVID-19 typically include fever, cough and difficulty breathing [3]. Recently six more symptoms of COVID-19 have been recognized including chills, repeated shaking with chills, muscle pain, headache, sore throat, and loss of taste or smell [4]. However, patients with COVID-19 may also present symptoms or abnormalities of multisystem, in addition to respiratory, including gastrointestinal [5], cardiovascular [6-9], urologic [7-11], hematologic [12-14], immunologic [8, 15-22], and the central (CNS) and peripheral (PNS) nervous systems [22-26]. Notably, individuals of any age, from infants to adults or seniors, can be infected with SARS-CoV-2 and may have typical, atypical or no symptoms [27-29]. Some patients may die suddenly without a preexisting comorbidity or risk other than proceeding SARS-CoV-2 infection. In this article we summarize clinical manifestations of COVID-19 involving multisystem and the possibly underlying mechanisms responsible for unexpected death.

SARS-CoV-2 Infection to Multisystem

SARS-CoV-2 infects humans through binding to a functional receptor, angiotensin-converting enzyme 2 (ACE2), on the cell membrane [30]. ACE2 exists in a wide variety of cells of various organs [31-36]. The wide distribution of ACE2 throughout the body (oral and nasal mucosa, nasopharynx, lungs, stomach, intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney and brain) predisposes humans to being susceptible to SARS-CoV-2 infection at a multitude of sites, rather than a single organ or system [32], resulting in diverse symptoms.

Overview COVID-19 Clinical Features

COVID-19 is primarily considered as a respiratory disorder [3]. Clinical presentations range from asymptomatic, through mildly symptomatic with or without common flu-like symptoms, to severe pneumonia [27-29] or critically acute respiratory distress syndrome (ARDS) requiring positive pressure oxygen therapy, mechanic ventilation and intensive care [37, 38]. Approximately 15% of patients are severe COVID-19 disease, and 5%-6% are critically ill with respiratory failure and/or multiple organ dysfunction or failure [38, 39]. There is a high mortality rate, particularly in elderly with preexisting comorbidities. In ARDS, multiorgan failure [28] and disseminated intravascular coagulation (DIC) may occur [40]. A combination of ARDS and DIC results in a death rate of 13.9% of COVID-19 patients [41].

Acute Respiratory Distress Syndrome (ARDS)

ARDS is characterized by severe edema of the alveolar wall and lung interstitium, corresponding to the ground glass appearance on thoracic CT imaging. ARDS is preceded by a marked rise of inflammatory molecules, including serum ferritin, C-reactive protein, D-dimers, and erythrocyte sedimentation rate. When DIC occurs, D-dimers levels further rise accompanying with liver and skeletal muscle enzymes and/or serum urea and creatinine, indicating ongoing multiorgan injury [14]. The lungs from patients with COVID-19 showed diffuse alveolar damage, interstitial mononuclear infiltrates, hyaline membrane formation, severe endothelial injury associated with the presence of intracellular virus, along with widespread thrombosis and microangiopathy in pulmonary vessels, which have been considered as the leading cause of death [42, 43].

Cardiovascular Involvement

SARS-CoV-2 causes myocardial injury, myocarditis, arrhythmias, acute myocardial infarction, heart failure and venous thromboembolic events resulting in significant mortality and morbidity [44, 45]. Of the COVID-19 sufferers with acute heart failure, nearly half were not known to have hypertension or cardiovascular disease [45]. Cardiac morbidities have been estimated in 22%-33% of hospitalized COVID-19 patients with increased troponin levels and electrocardiographic and/or echocardiographic abnormalities [46, 47]. Arrhythmias were observed in 17% and heart failure or cardiogenic shock in 33% of hospitalized COVID-19 victims [47]. SARS-CoV-2 virus has been detected in the hearts of patients died from COVID-19 [48].

Kidney

Acute renal failure (ARF, 27%-44%) or acute kidney impairment (AKI, 75%) were seen in COVID-19 patients, particularly in those of 60 years or older with comorbidities of hypertension and heart failure [7-11]. ARF lasted for average 12 days. Proteinuria, hematuria, and AKI often resolved within 3 weeks after the onset of COVID-19. Renal complications were associated with increased mortality in COVID-19 patients [9]. Postmortem histology showed evidence of severe acute tubular necrosis but no glomerular pathology or tubulointerstitial lymphocyte infiltration. Detection of SARS-CoV-2 and its nucleocapsid protein antigen in kidney tubules [8, 48] suggests that SARS-CoV-2 may directly infect human kidney, causing acute tubular damage and ARF. Notably, SARS-CoV-2 can be detected in the urine [3]. Possible transmission route by contamination with urine has been proposed. ARF has been considered as an independent risk factor for patients in-hospital mortality [7] and prognostic indicator for survivals with COVID-19 [8].

Liver

Approximately one third of COVID-19 patients presenting to hospital had mildly elevated liver tests but none developed overt liver failure. Liver test abnormalities could be multifactorial, such as the immune system-mediated inflammatory response, adverse effects of medications, and/or viral-induced cytopathic effects. Patients with abnormal liver functions were more likely to be male and had higher levels of procalcitonin and C-reactive protein [49]. Liver pathology showed minimally nonspecific periportal lymphoplasmacellular infiltration [42] and SARS-CoV-2 detected in the liver [48].

Gastrointestine (GI)

GI symptoms were reported in approximately 18% of COVID-19 patients and might precede, but most often concur with other COVID-19-related symptoms. The most common symptoms were anorexia (27%), diarrhea (12%), nausea and vomiting (10%), and abdominal pain (9%). They were more common in severe (17%) than less severe (12%) patients. Detection of SARS-CoV-2 RNA concomitantly in stool and respiratory samples could be seen in nearly half (48%) of COVID-19 patients and persistently positive stool viral RNA in 70% of patients even after respiratory tests had become negative, or in some COVID-19 patients without GI symptoms [50]. Possible fecal-oral transmission route has been postulated. Although both ACE2 receptors and viral nucleocapsid proteins in the gastric, duodenal and rectal glandular epithelial cells were abundantly present, GI-

endoscopy in one patient showed no evidence of damage to the GI epithelium [51]. Despite detectable viral RNA in stool for up to 22 days after negative swabs, the virus did not replicate [52].

Brain and CNS

Approximately 8%-36.4% COVID-19 patients may have nervous system–related clinical findings [25, 53]. These neurologic manifestations ranged from fairly specific symptoms, e.g. anosmia/hyposmia (smell impairment) or ageusia/dysgeusia (taste impairment), depressed level of consciousness, seizures, and stroke; to more nonspecific symptoms, e.g. headache, dizziness, sore, or fatigue [25]. The appearance of neurologic symptoms correlates to COVID-19 severities, more frequently in severe (45.5%) than less severe (30.2%) patients [22, 25]. Smell or taste impairment tended to appear early in the clinical course [25]. Notably, anosmia without congestion is a common early feature of COVID-19 [54]. Most strokes in COVID-19 patients were cryptogenic, possibly related to an acquired hypercoagulability or a cardioembolic source, often in young with worse outcomes because of delay in seeking appropriate care [55-59]. Brain-blood barrier could be breached in the course and SARS-CoV-2 detected in the brain [48]. Specific SARS-CoV-2 RNA was detected in cerebrospinal fluid in a patient with meningitis but not in nasopharyngeal swabs [24]. Brain imaging such as MRI studies showed evidence of meningitis, encephalitis and encephalopathy, indicating the possibility of SARS-CoV-2 induced pathology [23, 24].

PNS and neuropathy

Peripheral neuropathy in COVID-19 may be caused by SARS-CoV-2 direct invasion or cross-immunoreaction adversely against antigenic components of Schwann cells or axons, manifesting Guillain-Barré syndrome (GBS) or Miller Fisher syndrome [60-62]. The clinical course of GBS in COVID-19 patients can be indistinguishable from classic GBS [62-64]. Those GBS symptoms tended to occur 5-10 days after the first COVID-19 symptoms, exhibiting initial weakness in the legs and tingling or facial weakness, then evolving into generalized flaccid tetraplegia [62, 64]. Notably, GBS may even occur 7 days before the onset of COVID-19 symptoms and detection of SARS-CoV-2 from oropharyngeal swabs [61]. Lumbar puncture, when performed, showed increased protein in cerebrospinal fluid but no SARS-CoV-2 detected.

COVID-19 in Children

Children account for less than 2% of COVID-19 cases [28, 65-67]. The lower risk among children may be related to a low expression of ACE2 [68, 69] which is the receptor through which SARS-CoV-2 uses for host entry [30, 69, 70]. Indeed, age-dependent expression of ACE2 in nasal epithelium and kidney has been demonstrated [68, 71]. Clinically, children can be infected with SARS-CoV-2 as likely as adults, although they have fewer symptoms and less severe disease [65, 67]. A meta-analysis [72] showed that 83% of infants and children had a positive contact history, mostly with family members. The average incubation time was 7, ranging from 2 and 25, days. SARS-CoV-2 could be isolated from nasopharyngeal secretions (up to 22 days) and stools (more than 30 days). Co-infections (mainly mycoplasma and influenza) were frequently seen in 79% of children. Importantly, 35% of children were asymptomatic, which can serve as a source for spreading. The most common symptoms were cough (48%), fever (42%) and pharyngitis (30%) [72]. Laboratory findings were only minimally altered and chest imaging findings were nonspecific [72]. Children under 10 years were less likely to have a positive result in SARS-CoV-2 detection than were those 10 years or older and rarely needed intensive care (3%). Only a small number of deaths have been reported in children globally [72].

COVID-19 in Neonates

Detection of SARS-CoV-2 has not been reported in neonates [73-75] but identification of virus-specific antibodies was reported, suggesting the existence of a maternal-fetal transmission. In a small sample of 6 neonates born by cesarean to 6 mothers with confirmed COVID-19, SARS-CoV-2 was not detected by blood or throat swabs but elevated serum levels of IgG (in 5 of the 6) and IgM (in 2 of the 6). IgG is passively transferred across the placenta from a mother to fetus beginning at the end of the second trimester and reaches high levels at the time of birth [76] while IgM is not usually transferred from a mother to fetus because of its larger macromolecular structure it could be produced by the infant if the virus crossed the placenta [75]. The long-term effect, if any, of intrauterine infection with SARS-CoV-2 on infants remains to be investigated.

Skin Rash and COVID-Toes

Rashes with persistent fever, hypotension, multiorgan failure, and elevated inflammatory biomarkers, manifested as Kawasaki-like disease, were seen in children and adolescents with COVID-19 between 2-21 years old [77, 78]. The rash usually resolved spontaneously within a week and no virus could be isolated from the skin [79, 80]. Notably, Kawasaki disease is a rare inflammatory disease usually affects children younger than 5 years. The hallmark of Kawasaki disease is a persistent high fever (over 38.3°C or 101°F) for at least 4 days with rashes, conjunctiva congestion, swelling and redness to lips, tongue, neck, hands and feet due to severe inflammation. The underlying mechanism for the development of Kawasaki-like manifestations in COVID-19 children has been considered as a severe inflammatory syndrome linking to proinflammatory response and unified endothelial vascular injury in multiorgan systems triggered by SARS-CoV-2 infection. A term of multisystem inflammatory syndrome in children (MIS-C) has been named and warrants further investigation [77, 78, 81].

Itchy red bumps on the toes, and sometimes fingers are seen in some COVID-19 patients and referred to “COVID-toes”. COVID-toes may be a sign, and also a consequence,

of activation of the immune system in response to SARS-CoV-2 infection that causes inflammation involving small blood vessels of the skin. Inflammation may cause vasculitis and small vessel thrombosis [82-84]. Interestingly, COVID-toes are seen commonly in healthy and young individuals with COVID-19, and sometimes even patients did not know they were infected by SARS-CoV-2. Symptoms of COVID-toes may include painful, burning, or itchy bumps or a rash on their toes with frostbite appearance in various severities that can last for a week or occasionally up to three to four weeks. COVID-toes usually heal without treatment.

Cutaneous manifestations of COVID-19 appeared heterogeneously presented in up to 20% of patients with various severities of COVID-19. The skin lesions can be divided into five clinical patterns such as erythema with vesicles or pustules (pseudo-chilblain) (19%) in the acral areas of patients with less severe disease, or vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%) in more severe COVID-19 patients [85]. It has been proposed that the rash might be induced by an immune response due to high levels of proinflammatory cytokines.

Eyes

Individuals contracted SARS-CoV-2 may have ocular symptoms. Approximately 0.8% of COVID-19 patients develop conjunctivitis and watery eyes [3]. A physician was infected when only wearing an N95 mask without anything to protect eyes [86] suggesting SAR-CoV-2 may directly infect the eye.

Sexual Transmission

Because ACE2 is enriched in spermatogonia, Leydig and Sertoli cells of the testis [36, 87], it is not surprising that SARS-CoV-2 can be detected in the semen from the patients with COVID-19 in both acute and recovering phases [88], which raises the possibility of sexual transmission. Abstinence or condom use might be considered as a preventive means for these patients [88].

Host-Immune Responses

SARS-CoV-2 infection can induce an uncontrolled host-immune response, leading to a life-threatening condition called cytokine release syndrome (CRS). However, many findings in patients with severe COVID-19 are rarely observed in other respiratory viral infections, such as severe lymphopenia, extensive pneumonia and lung tissue damage, cytokine storms leading to ARDS and multiorgan failure [89]. Elevations of cytokines have led to the hypothesis that an immune-mediated cytokine storm, similar to CRS, is primarily responsible for the toxicity and end-organ damage mediated by SARS-CoV-2 infection [89]. Lymphopenia causes a defect in antiviral immunity and, simultaneously, a cytokine storm starts with extensive activation of cytokine-secreting cells with innate and adaptive immune mechanisms, both of which contribute to ARDS with a poor prognosis [39, 90]. A role for cytokine-driven neutrophil mobilization in COVID-associated lung toxicity may explain why neutrophilia, despite the absence of secondary bacterial infections, is associated with increased mortality [91].

High levels of pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-10, granulocyte macrophage-colony stimulating factor (GM-CSF) and G-CSF have been found in patients with ARDS [39, 89, 90]. Of note, TNF-α suppresses hematopoiesis, leading to cytopenia. Among pro-inflammatory cytokines, IL-6 appears to be profoundly involved, as indicated by simultaneously elevated C-reactive protein levels. Substantive evidence indicates that a dysregulated innate immune response contributes to the clinical presentation of patients with severe COVID-19, with enhanced circulating monocytes that secrete both IL-6 and IL-1β [20, 92, 93]. However, it is currently unclear whether elevated IL-6 is detrimental or beneficial in the COVID-19 course as IL-6 possesses dual actions by either suppressing [94] or facilitating viral replication [95]. Therefore, caution is warranted before invoking IL-6–mediated CRS as the sole pathological driver in COVID-19 [20].

Immunity and antibody

Lymphopenia is a consistent laboratory finding in COVID-19. Worsening lymphopenia correlates with clinical deterioration during COVID-19 course and poor prognosis [15, 16], whereas recovery of lymphocyte counts tends to precede clinical recovery [96]. T cell depletion in both lung-lodging and circulating have been observed in COVID-19 patients and in animals with chronic viral infections [8]. Additionally, single-cell sequencing of peripheral blood mononuclear cells of patients recovering from COVID-19 showed signs of clonal expansion, T cell activation and memory formation, which are consistent with an effective adaptive immune response [92]. The pathogenesis of COVID-19 is believed to proceed via both cytotoxic and immune-mediated mechanisms [17-20].

Anecdotal reports have shown encouraging outcomes on administrating convalescent plasma in patients with severe COVID-19. There is benefit on several clinical, biochemical, radiological parameters and prompt viral suppression. Importantly, no severe adverse effects were observed [97]. In general, the level of severity of COVID-19 correlates with the titers of antibody against SARS-CoV-2 [98]. Unfortunately, it has not always been found that higher titers of antibodies correlate with clinical improvement in COVID-19 [52, 99]. Moreover, mild symptoms can be resolved prior to seroconversion (as reflected by detectable IgM and IgG), although detectable IgM and IgG antibodies have preceded declines in SARS-CoV-2 viral loads [52, 99]. High IgM levels at early stage and high levels of IgG at late stage were frequently observed in patients with severe COVID-19. These observations suggested that, beside the antiviral efficacy, the antibody response might be associated with secondary

antibody-mediated organ damage. Using neutrophil-to-lymphocyte ratio and serum IgG levels detected at late stage has been proposed as a model of combined immune responses to predict disease severity and prognosis in patients with COVID-19 [100].

Antibody-Dependent Enhancement (ADE)

ADE is a phenomenon in which binding of a virus to non-neutralizing antibodies enhances its entry into host cells and promotes its replication [101]. Antibodies elicited by infection with one viral serotype may paradoxically promote both viral replication and an overly generous immune response upon exposure to a new viral serotype. Some cells of the immune system are infected without receptors on their surfaces that the virus uses to gain entry, but they have Fcγ receptors that bind to the Fc fragment of antibodies. For example, a virus gains entry to and infects the immune cell via binding Fc fragment of the antibody to Fcγ receptor on the cell membrane after the virus has been bind to the antigen-binding site of the antibody (Figure 1). Thus, a preceding infection with a different viral serotype with normally mild viral infection may become life-threatening [19].

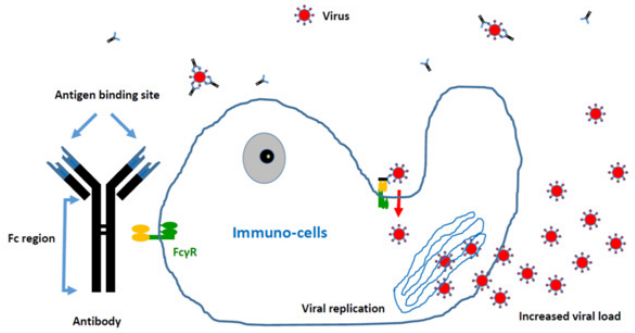

Figure 1: Schematic representation of antibody-dependent enhancement. Virions (such as coronavirus) are recognized by heterotypic antibodies from a previous infection. Complexes bind them to the Fcγ receptor (FcγR) on the surface of immuno-cells (e.g. macrophages), and internalized. The viral replication intracellularly leads to an increased viral load.

ADE has been proposed to account for the severity of COVID-19 [21]. Possibly, prior infection with other coronaviruses, from common cold to SARS, may have primed patients with COVID-19 and predisposed them, via ADE, to severe disease with lymphopenia once infected with SARS-CoV-2. Cross-reactivity of antibodies against the spike protein of SARS-CoV-2 and SARS-CoV has been demonstrated [102]. ADE leading to both increased infectivity and virulence has been observed with mosquito-borne flaviviruses such as dengue virus, yellow fever virus, zika virus; and with HIV or coronaviruses [103].

ADE may hamper vaccine development, as a vaccine may elicit production of antibodies which, via ADE, worsen the disease. ADE has been reported in human with SARS via antibodies induced by a SARS-CoV vaccine that enhanced infection of B cell lines [104] despite of protective responses in a hamster model. In fact, vaccine candidates for dengue virus and feline infectious peritonitis virus (a cat coronavirus) had to be stopped because they evoked ADE [105] and paradoxically increased the disease severity [103, 106, 107]. Thus, it has been cautioned that hasty development of such vaccines may be risky [108]. Rigorous research leading to a safe and effective vaccine production should be ensured [17, 21].

Disseminated Intravascular Coagulation (DIC) And Deep Vein Thrombosis (DVT)

DIC is an acquired syndrome characterized by intravascular activation of coagulation without a specific localization [109]. DIC simultaneously affects the coagulation system between coagulation and fibrinolysis, activating pro-coagulant and fibrinolytic cascades, causing consumption coagulopathy with abnormal laboratory findings of low platelets, low fibrinogen, high INR, and high D-dimer [110]. D-dimer has been considered to be linked to the severity and mortality in patients with COVID-19 [111, 112] and may serve as a surrogate biomarker for hemostasis and can be used an adjunct to guide the management of COVID-19 patients [113].

COVID-19 is likely a risk factor for DVT in hospitalized patients [111-116]. Prophylaxis for venous thromboembolism may be beneficial [113, 116]. The incidence and prevalence of arterial and, in particular, venous thromboembolic events diagnosed within 24-hours of admission are high in COVID-19 patients and are associated with adverse outcomes. DVT was estimated to occur in 25% of ICU patients with COVID-19 [114], even with anticoagulant prophylaxis [115]. Because of the widespread distribution of ACE2 in endothelial cells of blood vessels including large or small arteries and veins, SARS-CoV-2 can infect and damage the walls of vessels, activate the immune system, cause inflammation, result in vasculitis and abnormal hemostatic cascade leading to DIC and/or thromboembolic events [82, 83].

Pathologic Evidence

A German study on 27 autopsies showed SARS-CoV-2 infected many organs in addition to the lungs and pharynx [48]. SARS-CoV-2 levels were highest in the respiratory tract and also found in 17 hearts, 17 livers, 8 brains, and kidneys of 13 patients. Interestingly, among those without a history of kidney disease, SARS-CoV-2 was identified in 9 of 10 patients [48]. SARS-CoV-2 persistence in the respiratory tract was considered to be the leading cause of death in COVID-19 patients with and without invasive ventilation [42, 43].

Unexplained Sudden Death

Unexpected death was seen in patients with COVID-19, particularly in young without preexisting medical conditions. Notably, SARS-CoV-2 induced-myocarditis is a non-ischemic inflammatory form of myocardial injury, which can be caused by viral cytotoxicity or cytokine storm mediated-cardiomyopathy [117], leading to cardiac dysfunction, arrhythmias and sudden death. In autopsies, SARS-CoV-2 was detected in the hearts [48].

SARS-CoV-2 may complicate the unexpected death by dysregulation of central autonomic function. SARS-CoV-2 may invade the brain via three possible routes [70], i.e. directly through the olfactory epithelium, hematogenously via the areas of the brain that lack blood-brain barrier, and trans-synaptically passing through vagus nerve [70, 118]. ACE2, the functional receptor for SARS-CoV-2 infection, is expressed throughout the brain, notably in neurons of brainstem that control cardiorespiratory functions [118, 119]. Dysfunction of ACE2 in the brain causes hypertension, arrhythmias, heart failure and myocardial infarction [70, 119-121]. If ACE2 in the medulla oblongata is targeted by SARS-CoV-2, brainstem dysfunction of the cardiorespiratory center with loss of involuntary control of breathing may occur, leading to arrhythmias and cardiorespiratory arrest [3, 6, 70, 122]. Autopsies of patients died from COVID-19 showed the evidence of detection of SARS-CoV-2 nucleocapsid protein in the medulla, frontal lobes and olfactory nerves, which supports the postulation that SARS-Cov-2 infects brain [123]. The finding of SARS-CoV-2 infiltration in the brainstem raises the possibility that the pathophysiology underlying cardiorespiratory failure for sudden death in patients with COVID-19 may be related to CNS pathology [53, 122, 123].

SARS-CoV-2 induced-hyperinflammation may be a crucial mechanism responsible for the unexpected death in COVID-19 patients [39, 89, 90]. Excessive production of pro-inflammatory cytokines with subsequent downregulation of anti-inflammatory cytokines, i.e. interferon-γ, can be seen in, particularly critically ill, patients with COVID-19 [124]. Hyperinflammation, cytokine storm and diffuse vascular endothelial damage may produce extensive microangiopathy with thrombosis and DIC in many organs, clots in large and small arteries and veins [12, 125], resulting in multiorgan failure, myocardial dysfunction [126], pulmonary embolism [12, 13, 124], stroke [22, 23, 26], rapid deterioration, and sudden death [12, 13,].

Summary

The widespread distribution of ACE2 receptors allows SARS-CoV-2 to gain entry to various cells, making it possible for SARS-CoV-2 to attack many types of cells in various organs, and produce an array of symptoms, varying from infants to adults. SARS-CoV-2 infection-mediated cytotoxic effects, defect in antiviral immunity, hyperinflammation, cytokine storm and ADE contribute to COVID-19 severity, prognosis and sudden death in paralleling with multiorgan dysfunction.

Acknowledgments

The Authors are grateful to Professor Tim Lachman of Lewis Katz School of Medicine at Temple University, Philadelphia, PA; Professor Ganxin Yan of Lankenau Institute for Medical Research, Main Line HealthCare, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; Professor Linqiu Zhou of Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; and Dr. Haoli Jin of Mount Sinai Hospital, Icahn School of Medicine, New York, NY for reviewing this manuscript and helpful comments.

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