ACS Chemical
Neuroscience

Viewpoint

Fragile Endothelium and Brain Dysregulated Neurochemical Activity in COVID-19

Abdulrahman Alharthy, Fahad Faqihi, Ziad A. Memish, and Dimitrios Karakitsos*

Cite This: *ACS Chem. Neurosci.* 2020, 11, 2159–2162

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ABSTRACT: Immune system and renin-angiotensin-aldosterone system dysregulation with associated cytokine release syndrome may be a key feature of early stage of SARS-CoV-2 organotropism and infection. Following viral mediated brain injury, dysregulated neurochemical activity may cause neurogenic stress cardiomyopathy, which is characterized by transient myocardial dysfunction and arrhythmias. Cardiomyopathy along with acute acute inflammatory thromboembolism and endotheliitis (fragile endothelium) might at least partially explain the underlying mechanisms of rapidly evolving life-threatening COVID-19. Further studies are clearly required to explore these complex pathologies.

KEYWORDS: COVID-19, thromboinflammation, cytokine storm, neurogenic stress cardiomyopathy, renin-angiotensin-aldosterone system

INTRODUCTION

Recently, devastating brain injuries including stroke, intracerebral hemorrhage, and acute disseminated encephalomyelitis (ADEM) have been reported for the novel SARS-CoV-2 disease (COVID-19).[1,2] This injury has been linked to the ability of the virus to gain cell entry via subunits of its spike protein that after being primed by the cellular serine protease TMPRSS2 could bind to the angiotensin-converting enzyme 2 (ACE2) receptor, thus causing endothelial inflammation.[3,4] The pathophysiologic repertoire of SARS-CoV-2 integrates direct viral toxicity, endotheliitis, and thromboembolic phenomena, as well as a dysregulated immune response and renin−angiotensin−aldosterone system (RAAS). The immune pathogenesis may be further linked to the virus related cytokine release syndrome (CRS)[5] and associated microcirculatory dysfunction, which in turn is clearly documented as small vessel angiopathy with associated microthrombosis in autopsies.[6,7] Although recently published studies have suggested an increased prevalence of neurogenic stress cardiomyopathy (NSC) in patients with COVID-19,[8−10] the histopathologic findings in autopsies of deceased COVID-19 patients have not confirmed definitively the occurrence of myocarditis.[7] Moreover, in the natural course of severe COVID-19, there appears to be an *early stage* during which the virus may choose to attack any system (organotropism), and a *late stage* that is usually featured by diffuse lung injury (in the majority of cases).[11] We have previously demonstrated the natural course of COVID-19 lung injury by means of point-of-care lung ultrasound in a cohort of critically ill patients.[12] Herein, we are analyzing data regarding the *early stage* of COVID-19 focusing on endothelial injury and the associated neurochemical dysfunction.
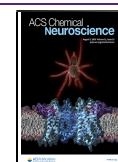
FRAGILE ENDOTHELIUM AND DYSREGULATED NEUROCHEMICAL ACTIVITY

The hallmark of the SARS-CoV-2 pathology appears to be endothelial damage. Apart from the aforementioned mechanisms of direct cell entry, dysregulation of RAAS and the immune system is considered to be important. The high affinity of SARS-CoV-2 for the ACE2 receptor, and possibly other receptors that are still to be identified, could result in severe dysfunction of the RAAS, as ACE2 is a pivotal counter-regulator in this pathway. RAAS is integrated in controlling essential homeostatic processes such as electrolyte/fluid balance, blood pressure, and vascular permeability. ACE2 cleaves angiotensin II into angiotensin I, which has vasodilator, antiproliferative, and antifibrotic properties.[13] The organotropism of SARS-CoV-2 could be at least partially explained by the hypothesis that the virus is using the RAAS as a vehicle of its unpredictable *early stage* attack on human cells. During this *early stage* of infection, lymphocytopenia, a key laboratory marker of COVID-19 and an early predictor of disease severity, may develop rapidly within days (as compared to years required by other viruses to cause immune system dysregulation, i.e., human immunodeficiency virus). Interestingly, viral ACE2-dependent toxicity has been one of the proposed mechanisms of lymphocytopenia, integrating abnormally high levels of D-dimer, neutrophilia, and the presence of atypical lymphocytes and megacaryocytes, signaling thus, according to previous studies, immune system dysregulation and associated CRS.[14] Subsequently, the increased expression
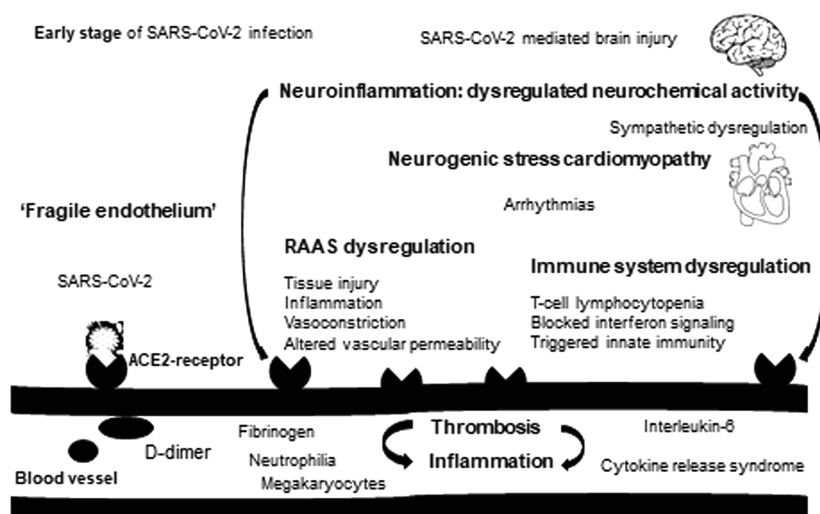
Figure 1. Theory of fragile endothelium (endotheliitis and thromboinflammation) and the dysregulated brain neurochemical activity in the early stages of SARS-CoV-2 infection (with brain tropism), resulting in neurogenic stress cardiomyopathy.

of ACE2 in endothelial cells post SARS-CoV-2 infection may disseminate a malicious cycle of endothelial inflammation, and associated thromboembolic phenomena (fragile endothelium, Figure 1). However, this cannot explain the elusive myocardial inflammation in histopathology findings of COVID-19 patients.[7] Surely, the pathophysiology of COVID-19 related cardiac injury could be multifactorial, integrating NSC, coronary artery disease, arrhythmias, right ventricular strain due to acute respiratory syndrome, and putative pulmonary embolism. Among the potential mechanisms, the suggested occurrence of NSC seems to be a rational thought. The fact that the virus may cause direct or indirect brain inflammatory injury has been underlined in the aforementioned paragraphs. The brain–heart interplay in the NSC pathophysiology has been studied previously. Catecholamine-mediated direct myocardial injury remains the mainstream hypothesis. Brain injury may elicit a catecholamine storm, which in turn may cause coronary artery dysfunction, epicardial vessel spasm, transient left ventricular outflow tract obstruction, and generation of coronary clots with spontaneous recanalization. The massive release of catecholamines has been also linked to a specific genetic basis such as polymorphisms of b1, b2, a2 receptors, Gs or Gi proteins, adenyl-cyclase, and other constituents of the adrenergic pathways.[15–17] Notably, the histopathology findings of ischemic heart disease versus NSC are different: in the former, cells die in an almost relaxed state characterized by polymorphonuclear cell response and necrosis; while, in the latter, cells may die in a hypercontracted state with contraction bands, which is usually visible adjacent to the cardiac nerves. However, in NSC, the myocardial abnormalities can also be reversible. Hence, this might be a focus of COVID-19 histopathology studies.

The pertinent neuroendocrine changes resulting in the catecholamine storm post brain injury are mediated via the hypothalamic–pituitary–adrenocortical and sympatho–adrenomedullary axes. Moreover, a network within the insular cortex, the anterior cingulate gyrus, and the amygdala has also been suggested to play an essential role in brain–heart interactions. This network is connected with the cerebral cortex, the basal ganglia, and the limbic structure. Interestingly, a lateralization model for cardiovascular function with sympathetic tone predominantly regulated in the right insula

and parasympathetic effects situated in the left insula has been previously suggested.[18–20] Nevertheless, the cardioregulatory sympathetic pathways also integrate the cortex, the amygdala, the periaqueductal gray, the locus coeruleus, the rostral and caudal ventrolateral medulla, the cingulate, the spinal lateral horn, and the nucleus tractus solitarii, which have been previously suggested to be prone to direct SARS-CoV-2 invasion.[21] We speculate that the documented ADEM in severe COVID-19 along with its pertinent structural brain distribution may further imply that the pathological involvement of the insula along with the hypothalamic–pituitary–adrenocortical and sympatho–adrenomedullary axes cannot be excluded in evolving SARS-CoV-2 infection with a brain tropism. This hypothesis may at least partially explain the fact of rapidly evolving clinical pictures and sudden death in critically ill patients with COVID-19.[22,23]

■ CONCLUSION

Immune system and RAAS dysregulation with associated CRS may be key features of the *early stage* of SARS-CoV-2 organotropism and infection. Dysregulated autonomic discharges, post brain viral injury, may cause NSC, which is characterized by transient myocardial dysfunction and heart-rate variabilities and could run a subclinical course. However, this dysregulated neurochemical activity along with the acute inflammatory thromboembolism and endotheliitis (fragile endothelium) might at least partially explain the underlying mechanisms of life-threatening COVID-19. Surely, further studies are clearly required to shed more light on these complex pathologies.

■ AUTHOR INFORMATION

Corresponding Author
  Dimitrios Karakitsos − *Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia;* orcid.org/0000-0003-3370-7099; Email: karakitsosdimitrios@gmail.com

Authors
  Abdulrahman Alharthy − *Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia*
  Fahad Faqihi − *Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia*

Ziad A. Memish − *Critical Care Department and Research and Innovation Center, King Saud Medical City, Riyadh, Saudi Arabia*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acschemneuro.0c00437

Author Contributions

All authors contributed to data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

Notes

■ LIST OF ABBREVIATIONS

COVID-19, SARS-CoV-2 disease; ACE2, angiotensin-converting enzyme 2; RAAS, renin−angiotensin−aldosterone system; ADEM, acute disseminated encephalomyelitis; CRS, cytokine release syndrome; NSC, neurogenic stress cardiomyopathy.

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