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Correspondence/Rebuttal

Letter to the Editor Regarding the Viewpoint "Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanism"

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Dear Editor,

I have read with interest the viewpoint entitled *Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanisms* by Baig et al.[1] This letter is supposed to supplement the aforementioned article with expanded scope on pathophysiological mechanisms which could prove salient in elucidating pathogenesis, seeking treatment, or considering clinical implications.

1. RECEPTORS FOR VIRAL ENTRY AND THEIR DISTRIBUTION

Besides the heart, kidneys, and testes having been found as initial sites of angiotensin-converting enzyme 2 (ACE2) expression, endothelial and neuronal presence was confirmed, with ultimate consensus stating the receptor is almost ubiquitous.[2,3] Although mRNA expression showed a clear presence of ACE2 receptor in various human neuronal regions, immunohistochemistry for ACE2 receptor of central nervous system (CNS) tissue, though with limited description, failed to show neuronal or glial positivity but did confirm it in the brain vasculature.[4] Translating the known about the severe acute respiratory syndrome coronavirus (SARS-CoV), it has been shown that full interaction of the virus with the ACE2 receptor is enabled once the viral spike protein is cleaved by surface proteases, namely, transmembrane serine protease 2 (TMPRSS2),[5] although some findings argue against the strict necessity of the step.[6] Moreover, lysosomal related components, namely, cathepsin L, 1-phosphatidylinositol 3-phosphate 5-kinase, and two pore channel-2 also have a role in initial viral interaction with the host cell.[6,7] An additional receptor binding the spike protein has been possibly recognized in CD147 by an in vitro experiment.[8] Both cathepsin L and CD147 are widely present in the CNS.[9,10] TMPRSS2 is only scantly present in the brain (brainstem, globus pallidus, insula, temporal lobe, occipital lobe, and postcentral gyrus).[11] A detailed study of nasal epithelium did not show TMPRSS2 presence in the neuronal component but did on the respiratory epithelium.[12]

Notably, SARS-CoV was confirmed in postmortem neurons and glial cells of human patients with fatal systemic manifestations.[13] A non-peer-reviewed report claims there was a case of symptomatic encephalitis with detected SARS-CoV-2 in cerebrospinal fluid.[14]

2. HOST–VIRUS INTERACTION ROUTES

The spread of the virus and the neuroinvasive potential have been proposed according to the known routes of SARS-CoV[15] and a growing body of findings specific for SARS-CoV-2.[16] Although hematologic spread is a known route for systemic viral dissemination, it has been postulated that the virus could also advance from the periphery to the CNS via retrograde neuronal transport and synaptic connections, notably vagal nerve afferents from the lung.[16] The concept of the pentapartite synapse as a nexus of endothelial, glial, neuronal, and immune cells opens a possibility for this mechanism.[17] However, with the growing findings of SARS CoV-2 infecting cells in the gastrointestinal tract,[18] the neuroinvasive potential could encompass the enteric nervous system and subsequent vagal and sympathetic afferents to the CNS. Previous experimental work on coronaviruses has shown retrograde neuronal transport as a viable route for viral invasion,[19] but it remains to be established for SARS-CoV-2 in particular. Exosomal cellular transport has also been shown as a mode of systemic viral dissemination, and it could include SARS-CoV-2.[20] Following SARS-CoV-2 infection and immune activation, $CD4^+$ T-cells produce granulocyte-macrophage colony-stimulating factor which further induces macrophage lines to secrete interleukin-6 (IL-6), occasionally causing a vicious cycle of cytokine storm, a most concerning clinical presentation. However, lymphatic spread of the virus via immune cells has not been postulated as no experimental data confirmed viral presence in these cells or the presence of ACE2 receptor[4,21]

3. CLINICAL PATHOPHYSIOLOGICAL IMPLICATIONS

Secondary neuroinflammation related to systemic immune activation could be mediated by lymphatic routes[22] which could contribute to encephalopathy, a common neurological manifestation of SARS-CoV-2 infection.[23,24] Per experimental experience with SARS-CoV, aside from this secondary neuroinflammation, primary neuronal infection results in

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increased secretion of IL-6,[15] an already recognized salient molecule implicated in cytokine storm. The aforementioned case of encephalitis may corroborate such a notion.[14] Additionally, systemic inflammation related metabolic and homeostatic derangements contributes to encephalopathy, but it may also predispose one to stroke, which has been noted to occur more commonly in severe clinical presentations.[25] Besides the acute neurological manifestations of SARS CoV-2 infection, further monitoring for long-term sequelae may reveal viral contribution in pathophysiology or increased risk for neuroinflammatory and neurodegenerative diseases. It has been shown in animal and human studies that coronaviruses could possibly be implicated in the pathogenesis of Parkinson's disease,[26] acute disseminated encephalomyelitis,[27] or multiple sclerosis.[23,28] In already established neurologic patients and even more so, those under active immunomodulating therapies, noticing trends in acute and chronic disease presentation or course may provide valuable insights in guiding acute management and determining the neuropathologic aspects of SARS-CoV-2. Exemplary neurologic features of SARS CoV-2 include anosmia and dysgeusia.[29] For the former, it could be argued it is more, or even exclusively, related to the respiratory epithelium infection and subsequent inflammation, but for the latter it still remains an open question. High expression of ACE2 was found on tongue epithelium,[30] but animal studies show ACE2 expression in the nucleus of the solitary tract,[31] which could point to central cause of dysgeusia and a possible neuroinvasive route by continuous local or retrograde vagal axonal transport. Further research is warranted, and this letter should supplement the original publication to expand the scope and understanding of pathogenesis, and posit some reasonable hypotheses that could be scientifically scrutinized.

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Notes

The author declares no competing financial interest.

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