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Insult to Injury-Potential Contribution of Coronavirus Disease-19 to Neuroinflammation and the Development of HIV-Associated Neurocognitive Disorders

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Abstract

Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 is responsible for a new coronavirus disease known as coronavirus disease-19 (COVID-19). SARS-CoV-2 reports neurotropic properties and may have neurological implications, and this creates another health burden for people living with HIV. As yet, the impact of COVID-19 on (neuro)inflammation and the development of HIV-associated neurocognitive disorders (HAND) is not fully known. Here, we reviewed preliminary evidence that provides clues that COVID-19 may exacerbate inflammatory mechanisms related to the development of HAND.

Keywords: COVID-19, SARS-CoV-2, coronaviruses, HIV-associated neurocognitive disorders, HAND, inflammation

Introduction

HIV-associated neurocognitive disorders (HAND) are consequences of the effects of HIV-1 within the central nervous system (CNS).[1,2] HAND are classified according to impairment severity, namely, asymptomatic neurocognitive impairment, mild neurocognitive impairment, or HIV-associated dementia.[3,4]

In the modern antiretroviral therapy (ART) era, the more severe forms of HAND have significantly decreased, however, milder forms are persisting in 50% of people living with HIV (PLWH).[5] Currently, the underlying neuropathophysiological mechanisms of HAND remain unclear. However, the common hypothesis for the persistence of HAND in the modern ART era is the continued immune activation and low-grade inflammation experienced by PLWH.[6] Regardless of viral suppression and CD4 count, HIV-positive participants report dysregulated inflammatory levels and the dysregulated levels are associated with HAND.[7–11]

Therefore, low-grade neuroinflammation may be a key pathway in the development of HAND. What are the implications for the development of HAND if another virus were to enter the CNS, eliciting a major immune response such as a cytokine storm and exacerbating the current low-grade inflammation in PLWH?

Since the first reported coronavirus disease-19 (COVID-19) case in December 2019, several studies have reported on the neurological implications of COVID-19.[12–18] Among several neurobiological mechanisms, increasing evidence suggests that COVID-19 may have an underlying neuroinflammatory pathology. Considering the large global (37.9 million) and African HIV populations (25.6 million),[19] it is important to assess the potentially detrimental effects of COVID-19 in these populations. This is especially true for neurocognitively impaired PLWH. The purpose of this review was to assess the potential contribution of COVID-19 to (neuro)inflammation and the development of HAND in PLWH.

HAND and (Neuro)inflammation

The neuroinvasion of HIV-1 into the CNS is explained by a widely accepted ''Trojan-horse hypothesis'' which states that HIV-1 is able to cross the blood/brain barrier (BBB) through infected monocytes, which later differentiate into macrophages.[20,21] HIV-1 is then able to act via several direct[22–24] and indirect mechanisms[25,26] to induce neuronal dysfunction and HAND. The neuropathogenesis of HIV-1 is well explained in a review done by González-Scarano and Martín-García.[2] This review focused on (neuro)inflammation, considering that it is a key pathway in the development of HAND in the modern ART era.

Once HIV-1 enters the CNS, it can further infect resident macrophages and microglia.[27–29] HIV-1 may also activate astrocytes, macrophages, and microglia resulting in an inflammatory phenotype that contributes to neuronal damage

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and the development of HAND.[2,25] Dysregulated inflammatory levels were reported in the blood,[9,30] cerebrospinal fluid (CSF),[31,32] and postmortem brain tissue[33,34] of cognitively impaired PLWH, supporting the role of aberrant immune regulation in the development of HAND.

Even with the introduction of ART, inflammatory levels do not return to that matching HIV-negative controls[35] and this low-grade inflammation may explain the persistence of milder forms of HAND. Inflammatory markers can impact neuronal health through several mechanisms. As an example, tumor necrosis factor-α (TNF-α) can induce BBB damage, which results in increased migration of infected cells into the brain,[36] dysregulate glutamate metabolism,[37–39] form reactive oxygen species,[40,41] and apoptosis in neurons.[42] Therefore, inflammation may directly contribute to neuronal dysfunction and the development of HAND. Furthermore, the presence of another virus within the CNS may contribute to the dysregulated inflammatory profile and exacerbate the development of severer forms of HAND.

Coronaviruses and (Neuro)inflammation

Although human coronaviruses (hCoVs) typically cause various respiratory diseases, coronaviruses (CoVs) are sometimes linked with CNS diseases such as multiple sclerosis and acute disseminated encephalomyelitis.[43–47] CoVs can target the CNS and cause nerve damage through direct infection pathways (viz blood circulation[48] and neuronal pathways[49,50]), hypoxia,[51] immune-mediated injury,[52,53] angiotensin-converting enzyme 2 (ACE2),[54,55] and other mechanisms (e.g., biological properties of the CNS).[56,57] However, this review focused on those mechanisms most relevant to the indirect underlying pathways of HAND (i.e., inflammation).

Middle Eastern respiratory syndrome-CoV and severe acute respiratory syndrome-CoV

Middle Eastern respiratory syndrome (MERS)-CoV was first linked to MERS in 2012.[58] Patients initially showed nonspecific symptoms, with general malaise, low-grade fever, chills, headache, nonproductive cough, dyspnea, and myalgia the most commonly reported.[59] However, several case reports have also linked MERS-CoV infections to various neurological disorders, including neuropathy, delirium, and acute cerebrovascular disease.[60–62] A larger study of 70 MERS patients also reported neurological symptoms, with the most common listed as confusion (18/70) and seizures (6/70). Unfortunately, there is little evidence for the presence of the MERS-CoV in the CSF from patients, making the association between MERS and neurological symptoms tenuous at the moment.[63]

The first case of severe acute respiratory syndrome (SARS)-CoV was reported in China, November 2002.[64] Patients generally presented with chills, headaches, muscular pain, diarrhea, and pneumonia.[65,66] Cases were also reported for neurological complications, which included seizures, dysphoria, vomiting, and stroke.[44,67–69] Evidence suggests that SARS-CoV can cross the BBB, as viral RNA was detected in the CSF[44,67] as well as postmortem brain tissue.[68] Even for SARS-CoV, these are rare clinical presentations, and, in some cases, these neurological symptoms could be possibly linked to a differential diagnosis. However, the detection of viral SARS-CoV RNA—unlike what is reported for MERS-CoV—in both CSF and autopsied brain tissue points to a neurotropic component for SARS-CoV infections.[63]

CoVs generally target epithelial cells of the respiratory and gastrointestinal tract[70] as these cells contain the ACE2 receptor, which is utilized by the virus to enter the host cell. However, invasion is not limited to these cell types alone. The ACE2 is expressed in several brain regions, including the brain stem, subfornical organ, rostral ventrolateral medulla, nucleus of the tractus solitarius, and paraventricular nucleus.[71] Furthermore, ACE2 was found in both neurons and glia.[71–73] Therefore, SARS-CoV may directly infect cells of the CNS and contribute to neuronal dysfunction. However, SARS-CoV may also affect neuronal health through indirect methods.

The pathology of SARS-CoV has been linked to inflammation. In SARS-CoV-infected mice, elevated levels of inflammatory cytokines were observed, including interleukin (IL)-6, interferon (IFN)-γ, chemokine ligand (CCL)2, and CCL12.[74–76] Experimental investigations showed that the replication and accumulation of SARS-CoV were integral causes of the elevated levels of inflammatory chemokine markers in wild-type mice.[77] In SARS-CoV-activated monocytes and granulocytes, alarmin expression was upregulated resulting in increased chemotaxis,[78] and this primes the cerebral microenvironment for inflammatory processes.[79] It was also found that in SARS-CoV-infected patients, genes encoding for lipocalin-2 (an acute-phase protein) were upregulated.[78]

In addition to the possibility of glia and astrocytes used for viral replication, resident CNS cells are involved in neuroinflammation.[80–82] Astrocytes and microglia exposed to CoVs (mouse hepatitis virus) showed that the severity of neurovirulence of the virus associated with its ability to induce the proinflammatory cytokines IL-12 p40, TNF-α, IL-6, IL-15, and IL-1β.[83] Glial cells of a SARS-CoV-infected patient who developed severe CNS invasion reported elevated monokine induced by IFN-γ [MIG/C-X-C motif chemokine ligand (CXCL)9] cytokine levels.[68] Brain sections showed an intense inflammation with $CD68^+$ macrophage infiltration, neuronal necrosis, diffuse brain edema, and reactive gliosis.[68]

Moreover, viral proteins were detected by immunohistochemistry in brain neurons and astrocytes.[68] Furthermore, CXCL10/IP-10 and CXCL9 were elevated in the blood of this patient.[68] Taken together, these studies suggest the potential involvement of both glia and astrocytes in the neuroinflammatory processes of SARS-CoV. Due to the novelty of COVID-19 (SARS-CoV-2), findings from these studies may provide clues to the neuroinflammatory mechanisms of SARS-CoV-2 and COVID-19.

Severe acute respiratory syndrome-coronavirus-2

A CoV classified as SARS-CoV-2 is responsible for a new CoV disease known as COVID-19.[84] COVID-19 frequently presents as a pneumonia syndrome, with symptoms including fever, dry cough, and breathlessness reported most often.[84] Even though complications associated with the respiratory system are the most common and life-threatening in COVID-19, increasing evidence suggests that COVID-19 pathophysiology may also involve the central and peripheral nervous systems.[63]

A retrospective study of a possible neurological component to COVID-19 looked at data from more than 200

individuals in China. Due to an as yet unknown cause, patients—in particular those with severe COVID-19—exhibited symptoms that included impaired consciousness, skeletal muscle injury, hypogeusia, hyposmia, and acute cerebrovascular disease. Unfortunately, at the time of publication, all patients were still hospitalized and the association between these neurological symptoms and patient outcome could not be investigated.[85]

In another study, Li *et al*. report the development of acute cerebrovascular disease, including ischemic stroke, cerebral venous sinus thrombosis, and cerebral hemorrhage in a cohort of 13 COVID-positive patients. Interestingly, here again, the neurological symptoms were more common in severe cases of COVID-19, and also in older patients.[86] A third study, this time from France, also reports various neurological and neuropsychiatric illnesses in 84% of 58 COVID-19-positive patients admitted to hospital with acute respiratory distress syndrome (ARDS). For this cohort of patients with severe COVID-19, the authors report neurological features that include evidence of encephalopathy, corticospinal tract dysfunction, agitation, and delirium. Moreover, two patients had evidence of a small acute ischemic stroke.[87]

Likewise, many individual case reports describing the development of acute neurological disorders in COVID-19-positive patients, ranging from Guillain–Barré syndrome[88–96] to meningoencephalitis,[97] ischemic stroke,[98] acute necrotizing encephalopathy,[99] and acute hemorrhagic necrotizing encephalopathy,[97,99,100] are now being published.

How, and if, SARS-CoV-2 infects the CNS in patients has still not been proven definitively. However, Baig *et al*. have speculated that ''SARS-CoV-2 neurotropism occurs via a circulatory and/or an upper nasal trancribrial route.'' This would enable the virus to reach the brain, where it then binds and engages with the ACE2 receptors via the spike protein, followed by entry into the brain.[101]

On the contrary, *in vitro* studies are now showing that SARS-CoV-2 can infect and cause pathologies in brain organoid models. In a very recent study, pseudotyped SARS-CoV-2 viral particles were reported to infect human embryonic stem cell-derived brain organoids, as well as monolayer cortical neurons.[102] In another *in vitro* model of human brain organoids, evidence of SARS-CoV-2 infection—with accompanying metabolic changes in the infected and neighboring neurons—was reported.[103] Interestingly, it was suggested that SARS-CoV-2 preferably targets the soma of cortical neurons, but not neural stem cells, and that SARS-CoV-2 exposure is associated with missorted Tau from axons to soma, hyperphosphorylation, and apparent neuronal death.[104] These too are suggestive of neurodegenerative-like effects.

What are the possible mechanisms of the various neurological symptoms linked to severe COVID-19? Groups speculate that mechanisms could include the following: (1) direct viral neuronal injury; (2) a secondary hyperinflammation syndrome; (3) para- and postinfectious inflammatory or immune-mediated disorders; or (4) a severe systemic disorder with neurological consequences; these mechanisms could possibly act either individually or in combination.[105–107] On the contrary, even with the mounting evidence, not all researchers are convinced by the data. As an example, Larvie *et al.* question the interpretation of the data and the conclusions made in the report by Helms *et al*., speculating that the findings ''may not definitively indicate a specific syndrome of brain involvement associated with SARS-CoV-2.''[87,108]

The neuropathogenesis of COVID-19 is not clearly understood, however, SARS-CoV-2 belongs to the same beta-CoV clade of the previously reported SARS-CoV and MERS-CoV.[109] SARS-CoV-2 also shares several similarities to that of SARS-CoV and prior research of SARS-CoV may provide insight into COVID-19. Similar to SARS-CoV, the neuroinvasion of SARS-CoV-2 into the CNS may be by ACE2.[110,111] The SARS-CoV-2 receptor-binding domain (RBD) has a higher ACE2 binding affinity than SARS-CoV RBD. The ACE2 binding affinity of the entire SARS-CoV-2 spike is comparable with or lower than that of SARS-CoV spike, which suggests that the SARS-CoV-2 RBD, although more potent, is more occluded than the SARS-CoV RBD.

Compared with SARS-Co-V, cell entry of SARS-CoV-2 is preactivated by proprotein convertase furin, and thus, SARS-CO-V-2 has reduced dependence on target cell proteases for entry. These suggest that SARS-CoV-2 may maintain efficient cell entry while evading immune surveillance.[112] This may explain why SARS-CoV-2 may be a more virulent strain. It has also recently been suggested that SARS-CoV-2 may use integrins as an alternative cell receptor into host cells. SARS-CoV-2 may bind to integrins via a conserved RGD (403–405: arginine/glycine/aspartate) motif that is present in the RBD of the SARS-CoV-2 spike protein. This motif is present in all SARS-CoV-2 sequences analyzed to date.[113]

The findings for the presence of SARS-CoV-2 within the CSF have been contradictory. Certain studies show that COVID-19 patient CSF samples were polymerase chain reaction negative for the presence of SARS-CoV-2,[87,114–116] whereas others report SARS-CoV-2-positive CSF findings.[97,117,118] Furthermore, SARS-CoV-2 was detected in the capillary endothelial and neuronal cells of frontal lobe postmortem brain tissue.[119] These findings are similar to that reported for SARS-CoV, supporting the potential of the virus to breach the BBB. In patients recovering from ARDS and/or pneumonia, a large number experience cognitive impairment with impaired functional status, often persisting months after hospital discharge.[120,121] This may suggest an underlying neuropathology and it is postulated that neuroinflammatory processes may also be associated with such neurological complications in COVID-19 patients.[122,123]

SARS-CoV-2 causes a surge of inflammatory cytokines also known as the cytokine storm syndrome (CSS). Systemic CSS results in a significant release of cytokines, chemokines, and other inflammatory signals. CSS may damage the BBB, which allows further infiltration of cells into the CNS resulting in an amplified neuroinflammatory process.[123,124] The immune dysregulation[125] caused by SARS-CoV-2 results in upregulation of several genes that enhance proinflammatory and oxidative responses, resulting in inflammatory stress[78] and cytokine storm.[84,126,127]

SARS-CoV-2 is responsible for the persistent release of inflammatory markers, including IL-1β, IL-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-17, IL-18, IL-33, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1A (MIP-1A), MIP-1B, macrophage colony-stimulating factor (M-CSF), TNF-α, transforming growth factor-β, IFN-α, IFN-β, IFN-γ, and chemokines, including CCL2, CCL3, CCL5, CCL7, CCL12,

CXCL8, CXCL9, and CXCL10, which are ultimately responsible for the development of CSS.[84,128–132]

Moreover, the levels of inflammatory markers are related to the severity of COVID-19 infection, with elevated plasma cytokines/chemokines IL-1β, IFN-γ, CCL2, and IP-10 linked to mild-to-moderate cases and elevated levels of TNF-α, IL-8, IL-10, G-CSF, CCL2, MIP-1A, and IP-10 related to severer cases.[84,133] Several studies also reported elevated levels of C-reactive protein (CRP) in COVID-19 patients.[134–136] It was also found that VEGF (immune-related marker associated with inflammation) is dysregulated in COVID-19 patients, and could possibly be related to neuroinflammation and BBB damage.[137] Interestingly, in the majority of studies, IL-6 is elevated in COVID-19 patients.[17,84,133,138–140]

It is speculated that SARS-CoV-2 may activate resident astrocytes and glial cells. Currently, there is no evidence for the SARS-CoV-2 presence in astrocytes, however, there is a possibility for infection, activation, as well as astrocytes being viral reservoirs as shown in several studies of CoVs.[48,68,83,141,142] Similar to other neurotropic viruses,[53] SARS-CoV-2 may similarly induce the production of inflammatory markers such as IL-6 from glial cells that result in CSS.[83] SARS-CoV-2 within the CNS activates $CD4^+$ cells, in turn inducing macrophages to secrete IL-6 by producing GM-CSF.[130] The effect of SARS-CoV-2 on cells of the CNS is incompletely known, however, based on findings of other CoVs, SARS-CoV-2 may significantly increase inflammation within the CNS.

Potential Contributions of COVID-19 to (Neuro)inflammation in PLWH

Should COVID-19 contribute to (neuro)inflammation, what may this mean for patients with HAND who already experience dysregulated (neuro)inflammatory levels?[7,9,10,30,143] Preliminary evidence suggests that COVID-19 may exacerbate systemic and neuroinflammation, with common findings reported for IL-6. IL-6 is a predominant component of CSS and the pathway of IL-6 dysregulation may be important in the pathophysiology of COVID-19.[144,145] Prior HIV studies found dysregulated peripheral[8,146,147] and CSF[148] IL-6 levels to be associated with HAND. The effect of SARS-CoV-2 within the CSF may result in significantly higher levels of IL-6, which may negatively affect neuronal health in coinfected PLWH.

It was also shown that HIV-positive participants have elevated GM-CSF in CSF[149] and these elevated levels are associated with HAND.[148] Alternative markers which may also be dysregulated in patients with COVID-19, include CRP,[134–136] VEGF,[137] and lipocalin-2.[78] CRP is an inflammatory marker that has also been associated with domain-based and global HAND.[150] VEGF is suggested to regulate neuroinflammation and BBB dysfunction in COVID-19.[137] A prior study in PLWH reported that elevated CSF levels of VEGF were associated with HAND.[151]

Furthermore, lipocalin-2 gene expression was upregulated in SARS-CoV patients and may similarly be reflected in patients with SARS-CoV-2.[78] Previous work done by our group and others reported that peripheral lipocalin-2 levels were elevated in HIV-positive participants, and were associated with domain-based neurocognitive impairment[152] and thinner bilateral orbitofrontal cortex.[153] Furthermore, lipocalin-2 was upregulated in the neocortex of HIV-positive participants with brain pathology.[154] Therefore, the upregulation of lipocalin-2 due to COVID-19 may have detrimental effects in PLWH and HAND. Overall, the effects of COVID-19 may further add insult to injury by contributing to the dysregulated (neuro)inflammatory profile in PLWH. This may increase the likelihood of participants developing severer forms of HAND (i.e., HIV-associated dementia).

Anticytokine therapies and/or immunomodulators are considered potential therapeutic strategies to target the overactive cytokine response. This may provide relief for systemic inflammation, but will the same apply for therapies with limited CNS penetration? Even though a study has shown that treatment with the anti-IL-6 drug, tocilizumab (IL-6 receptor blocker), resulted in improvement of critically ill COVID-19 patients,[155] it may have limited benefit in the CNS if the brain is a viral reservoir for SARS-CoV-2.[156] In a clinical trial of tocilizumab for residual symptoms in schizophrenia,[157] results found no evidence that affects behavioral outcomes in schizophrenia. One potential explanation was the inability of this agent to penetrate the CNS.

Even though unlikely, another concern for SARS-CoV-2 coinfected PLWH is that the presence of SARS-CoV-2 could potentially result in an immune activation that may promote the reactivation of latent HIV.[158] The immune system may be activated by SARS-CoV-2 antigens, which may promote the reactivation of latent HIV as indicated by the appearance of HIV in ART-experienced PLWH (HIV surge). The HIV surge may increase the HIV reservoir and inflammatory profile and further accelerate the course of HIV-associated comorbidities (e.g., cognitive disorders).

Findings for studies between CoVs and HIV are contradictory. Initial studies reported that SARS-CoV[159] and MERS-CoV[160] coinfected HIV patients have a lower risk of CoV infection and progression to severe disease. However, the mechanisms responsible for this are not understood and it is not clear whether HIV replication may interfere with CoV replication and/or the effect of ART on CoV disease progression.[159] It was shown that immunosuppressed (low CD4 counts) HIV-positive participants may be protected from developing the cytokine storm observed in patients with COVID-19.[161]

Opposing views have also been argued and reported that neither the CD4 count[162] nor the use of specific antiretroviral drugs[161–163] affected the SARS-CoV-2 severity or infection rate. Limited findings exist for studies of SARS-CoV-2 and HIV in general[164] and no studies at this time for SARS-CoV-2 and HAND. Due to this, there is still much controversy and uncertainty, which require further investigation. There is a need for clinical and preclinical studies assessing the following: (1) CoV disease progression in PLWH in general, (2) the effect of ART on CoV disease progression, (3) the immune response (e.g., inflammation) in coinfected participants, and (4) the inflammatory response of CNS cells exposed to SARS-CoV-2.

Conclusions

Here we reviewed the potential contributions of COVID-19 to the development of HAND. Recent findings suggest that (1) COVID-19 has neurological implications, (2) CoVs (including SARS-CoV-2) may elicit a significant systemic immune response, and (3) may cross the BBB. Last, it may be speculated that CoVs (including SARS-CoV-2) may

similarly elicit inflammatory responses within the CNS and this may exacerbate neuroinflammation in PLWH. Therefore, COVID-19 may exacerbate the underlying neuropathology contributing to the development of severer forms of HAND.

Author Disclosure Statement

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