Parallels Between NeuroHIV and NeuroCOVID-19: Considerations for a Post-COVID-19 Era

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The coronavirus disease 2019 (COVID-19) pandemic has demonstrated the importance of cognitive and neuropsychological health, particularly the ability to keep one’s cognitive abilities sharp. For example, Xie et al. (2020) found that a better working memory was associated with greater compliance with social distancing, an important protective behavior. Yet, one of the many potential negative downstream effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is neurological complications, potentially affecting ~30% of people infected by the virus (Helms et al., 2020).

The immediate and long-term impacts of SARS-CoV-2 infection continue to unfold. Evolving alongside these discoveries is a better understanding of the SARS-CoV-2 impact on specific clinical populations, such as people living with HIV (PLWH). One potential area of overlap to consider is the neurological and cognitive effects of both infections. The purpose of this commentary was to start this dialogue; it is important to review and synthesize what we know about neuroHIV and neuroCOVID, make recommendations for clinical practice and research, and consider how these factors will interact moving into a post-COVID era. Briefly, parallels between neuroHIV and neuroCOVID are drawn in several areas, including inflammation and neuroinflammation, viral damage, adverse treatment effects, and gut dysfunction.

NeuroHIV and Cognition

Early in the HIV epidemic, alongside frank immunological compromise, neurological sequelae in PLWH frequently manifested as cognitive impairment that ranged from mild to severe. Antiretroviral therapy (ART) made it possible for PLWH to achieve viral suppression and greater sustained immune function, which has significantly diminished the severity of cognitive impairments. Today, for example, only 2% of PLWH experience HIV-associated dementia (Waldrop et al., 2021) compared with 15% in the early years of the epidemic (McArthur et al., 1993). Still, the prevalence of mild-to-moderate cognitive impairments (e.g., HIV-associated neurocognitive disorder [HAND]) remains high, affecting between 30% to 50% of PLWH. HAND is defined as a collection of cognitive symptoms whereby an individual scores 1 or more SDs below the norm-based (age, education, sex, and race) mean on cognitive performance tests in two or more cognitive domains (e.g., executive functioning, verbal memory, and psychomotor functioning; Waldrop et al., 2021). HAND can emerge from a variety of synergistic factors, including age-related brain changes, comorbid physical conditions, psychiatric conditions, and social factors (e.g., stigma and social withdrawal).

By 2030, approximately 70% of PLWH will be 50 years and older (Wing, 2017), and as they age, they become more vulnerable to age-associated comorbidities, including cardiovascular disease (78%) and diabetes/insulin resistance (17%), than those without HIV. Furthermore, 28% of PLWH will present with three or more comorbidities (Smit et al., 2015). These comorbidities negatively affect brain health, which can contribute to the detrimental cognitive effects of both neuroHIV and age-related cognitive declines (Cody & Vance, 2016). Accompanying these comorbidities, we expect an increased prevalence and severity of cognitive impairments.

Mental health symptoms and disorders can also contribute to HAND and are a major concern in PLWH, who also experience a high prevalence of anxiety (prevalence 28%), depression (prevalence 33%), and loneliness (prevalence 46%; Lowther et al., 2014). Compounding the impact of mental health symptoms
and disorders on quality of life, such prolonged emotional distress, stimulates the hypothalamus–pituitary–adrenal (HPA) axis to produce cortisol, which, over time, increases systemic inflammation. Inflammation, in turn, is known to damage the brain and impair cognition (Cody & Vance, 2016). As part of the stress response, it is important to promote strategies that reduce the stress response created by mental health issues to mitigate the damage that stimulating the HPA axis can cause.

HIV-specific contributors to HAND include inflammation and ART itself. First, HIV itself crosses the blood–brain barrier through infected monocytes; once there, it inflicts glial cells, which support the health and function of the neurons. As the glial cells die, they secrete neurotoxic molecules that damage the neurons (Cody & Vance, 2016). Second, HIV is considered a “slow burner” inflammatory disease. Although ART is effective in keeping the virus from replicating, it continues to stimulate the immune system, mounting a continual inflammatory response. Over time, such constant inflammation damages tissue, including the brain (McArthur & Johnson, 2020). Third, most studies show that HIV ART protects the brain and cognition from the effects of HIV (Caban et al., 2017), even though some of the HIV medications (e.g., abacavir, efavirenz, atazanavir, etravirine, and nevirapine) can exert neurotoxic effects (Cody & Vance, 2016). Although it is important for overall health to remain on ART, one seminal study showed that in a sample of 167 PLWH who were immunologically stable, after introducing an interruption of ART, cognition improved over a series of weeks (Robertson et al., 2010). Finally, gut dysregulation (i.e., microbial translocation) is a common condition caused by chronic inflammation of the gastrointestinal epithelial barrier. HIV has an attraction for Th17 type CD4+ T cells located in the gut-associated lymph tissue. These T cells are rapidly depleted during HIV infection, resulting in the release of cytokines. Over time, this also creates chronic inflammation (Ceccarelli et al., 2019) and is associated with poorer brain health and cognitive impairment in PLWH (Valdes et al., 2016).

**NeuroCOVID and Cognition**

As research on SARS-CoV-2 progresses, the extent to which this disease affects cognition in the short- and long-term remains unclear. Yet, it is clear from early evidence, in addition to the characteristic respiratory symptoms, there are clear direct and indirect effects of SARS-CoV-2 on brain health and cognition (Troyer et al., 2020). An early description of 217 hospitalized patients in Wuhan, China, reported a variety of neurological manifestations in nearly half of those with more severe infection, including encephalopathies, cerebrovascular injuries (e.g., stroke), and neuromuscular injuries (Mao et al., 2020). Similarly, in a retrospective report on SARS-CoV-2 patients from Wuhan, alterations in consciousness and encephalopathy were observed in 20% of those who died from SARS-CoV-2 (Chen et al., 2020). In yet another report, delirium was reported in nearly 24% of hospitalized SARS-CoV-2 patients (Lovell et al., 2020).

Severe acute respiratory syndrome coronavirus 2 may have both direct and indirect effects on brain health and cognition. First, the virus itself may directly affect neurons, as observed with SARS-CoV-1 patients, spreading from the respiratory tract to the central nervous system; similar viruses have been shown to demyelinate neurons and induce neuronal cell death (Troyer et al., 2020). Second, SARS-CoV-2 and similar viruses are known to create an acute inflammatory response, causing hypercytokinemia. In fact, proinflammatory cytokines (e.g., interleukin [IL]-6, IL-8, IL-10, tumor necrosis factor-alpha) have been significantly higher in patients with coronaviruses who do not survive (Chen et al., 2020). Such high levels of proinflammatory cytokines may promote encephalitis, as well as kidney and heart problems. These secondary problems can also contribute detrimentally to poor brain health and cognitive impairment. Third, SARS-CoV-2 patients with extreme respiratory distress undoubtedly suffer from hypoxia, depriving the brain and other vital organs of oxygen. Related to this, the most severely ill SARS-CoV-2 patients must be put on a ventilator. Yet, studies on acute respiratory distress syndrome indicate that the longer one is on a ventilator, the more likely one is to suffer from delirium and cognitive impairment, sometimes never returning to full premorbid cognitive status (Sasannejad et al., 2019), a condition commonly referred to as post–intensive care unit damage/syndrome. And fourth, gut dysregulation is observed in nearly 40% of SARS-CoV-2 patients (Zhang et al., 2020). Although the extent to which SARS-CoV-2 infiltrates the intestinal epithelium lining is unknown, theoretically such dysregulation may disturb the delicate microbiota–brain–gut axis, resulting in an array of neuropsychiatric manifestations, including cognitive impairment.

In addition, SARS-CoV-2 may be indirectly contributing in some way to poorer brain health in nonpatients as well as patients. First, social distancing and social isolation, by definition, limits interactions with others. Social interactions are known to stimulate the brain in ways important for promoting and maintaining cognition (Segel-Karpas & Lachman, 2018). Second, the pandemic has been a highly stressful time, with many individuals concerned about becoming ill, finances,
caregiving for others, and experiencing new roles. As with primary inflammation, such stress can increase cortisol production through overactivation of the HPA axis, resulting in both systemic and neuroinflammation (Cody & Vance, 2016; Waldrop et al., 2021).

**Synthesis of NeuroHIV/NeuroCOVID**

We can hypothesize regarding possible effects of COVID-19 on PLWH who are already affected by impaired brain health and cognitive deficits. First, both HIV and SARS-CoV-2 exert some negative impact on the central nervous system; HIV affects glial cells that support the neurons, whereas SARS-CoV-2 may affect neurons directly and could induce demyelination. It seems likely that additional neurological insults from SARS-CoV-2 could exacerbate cognitive decline in PLWH with already diminished cognitive reserve (Levine et al., 2020).

Second, systemic inflammation and, likely, neuroinflammation is clearly present with both HIV and SARS-CoV-2 (Levine et al., 2020). Although HIV-related inflammation is relatively low and chronic, SARS-CoV-2 causes a higher, more acute inflammatory response. Together, these inflammatory processes (i.e., “cytokine storm”) could potentially increase short-term damage above that experienced in SARS-CoV-2 patients without HIV. In contrast, PLWH who have a suboptimal immune system may in some ways fare better in response to SARS-CoV-2 infection because they may be less likely to suffer from the central nervous system damage caused by hypercytokinemia (Zhao et al., 2020). If they can weather such SARS-CoV-2-induced “cytokine storms” relatively well, without their immune system being overtaxed, they may experience less neuroinflammation.

Third, gut dysregulation in HIV is well documented, and such evidence for similar gut dysregulation is emerging in SARS-CoV-2. As seen in HIV, plasma sCD14, a proinflammatory marker of microbial translocation, correlates with cerebrospinal fluid sCD14 and neurofilament light chain protein, markers of axonal damage (Jespersen et al., 2016). In fact, higher levels of sCD14 in SARS-CoV-2 patients are associated with longer days spent in the intensive care unit (Zaninotto et al., 2020). Such inflammation also causes perturbations in the gut microbiota. Given the connections among the components of the microbiota–brain–gut axis, this perturbation in gut microbiota can compromise brain function. Such dysregulation of the microbiota–brain–gut axis has been associated with the development of neurodegenerative diseases, as well (Quigley, 2017).

For PLWH who contract SARS-CoV-2, these conditions may synergistically interact to further compromise neurological function and cognition, especially if they clinically manifest with COVID-19. Microbial translocation already present in PLWH may be exacerbated by SARS-CoV-2, thus creating more inflammation (Ceccarelli et al., 2019; Zhang et al., 2020). These effects might then be compounded by the direct effect of both viruses on the nervous system itself. And finally, the severity of illness, treatment required (e.g., ventilation), and degree of hypoxia are all factors further aggravating this unfortunate process.

For PLWH who do not contract SARS-CoV-2, this pandemic also exerts a negative impact on brain health and cognition. Probably the most obvious impact is related to mental health threats from isolation due to social distancing and increased stress. Social distancing has become a new cultural norm, and although some social interaction continues via social media, the amount and quality of such interaction is less than normal and may have more severe consequences for those already experiencing reduced social engagement due to HIV-related stigma. Several studies demonstrate that social interaction provides vital stimulation for the brain, such that a reduction in the amount or quality, especially during a period of high anxiety, can result in poorer cognition (Bzdok & Dunbar, 2020). For example, in a sample of 134 aging PLWH, Fazeli et al. (2014) observed that participants who were more socially engaged were less likely to experience cognitive impairment. During this pandemic, individuals without social resources and social engagement can experience feelings of loneliness and isolation, leading to increased stress that, in turn, stimulates the HPA axis, resulting in poorer cognition.

**Implications for Nursing Practice and Research**

Although we anticipate highly effective vaccines of nearly 95% and improved treatments in the near future (Olliaro, 2021), the cognitive intersection between HIV and COVID-19 emphasizes several issues relevant to clinical practice and treatment for all PLWH, whether or not they were directly infected with SARS-CoV-2. First, for practice, cognition in PLWH may be compromised by stress and isolation, whether resulting from the pandemic or another cause. For those infected with SARS-CoV-2, the infection itself and certain treatments (e.g., ventilation) may leave residual or long-term effects for months or even years. In either case, for many PLWH who are already cognitively vulnerable, assessment and monitoring of cognitive function should be considered during routine clinic visits (Waldrop et al., 2021). From a clinical and research perspective, the long-term effects of
SARS-CoV-2, in both preventive measures and long-term disease sequelae, remain unknown.

Second, from both a clinical and a research perspective, strategies are needed to protect brain health and/or remediate for cognitive loss (for a review of such strategies, see Waldrop et al., 2021). Several strategies are already being considered, but most focus around the concept of brain health literacy. A large body of literature shows that lifestyle factors such as physical activity, intellectual exercise (e.g., cognitive training), social stimulation, sleep hygiene, stress reduction, and good nutrition support brain function and boost cognition. Unfortunately, as shown in two studies (Vance et al., 2017; Woods et al., 2020), older PLWH, as a group, have little brain health literacy, which is knowledge about how to protect and improve neurological functioning and cognition, especially as people age. Therefore, educating patients about how to improve their brain health represents a strategy to protect and possibly improve cognition, both during and after SARS-CoV-2 infection.

Third, as both SARS-CoV-2 and HIV disrupt the microbiota–brain–gut axis and the microbiome, this represents another area of clinical practice and research. Some studies already suggest the role of prebiotics and probiotics in restoring the microbiome and reducing inflammation (Ceccarelli et al., 2019; Walton et al., 2020). Such a nutritional intervention is expensive and widely accessible.

Finally, the COVID-19 pandemic has challenged the social and psychological resources of PLWH. The need to develop and rely on resilience resources has become obvious, although resilience (i.e., grit, hardiness) has also been shown to affect cognition (Fazeli et al., 2019). In a sample of 120 PLWH and 94 adults without HIV, Moore et al. (2018) observed that for only PLWH, higher levels of grit (i.e., perseverance in reaching a passion or goal) was associated with less cognitive decline. Thus, strategies to help restore and build resilience in PLWH are needed (Fazeli et al., 2021). Such forays into positive psychology should be considered not only for protecting cognitive health (Randolph, 2018) but also for promoting mental health in PLWH for those with and without COVID.

Moving Into a Post-COVID Era

There are many parallels between neuroCOVID and neuroHIV; this brief commentary highlighted a few, but this is by no means exhaustive. As SARS-CoV-2 vaccines and treatments become more accessible, this period in our history has shown vulnerabilities in many areas, including cognitive health in PLWH. As PLWH are already cognitively vulnerable, it will become even more important to monitor cognitive functioning and consider strategies to ameliorate brain health and promote resilience moving into the post-COVID-19 era.

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Author Contributions

All authors listed met the ICMJE authorship criteria: (a) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting the manuscript or revising it critically for important intellectual content; (c) final approval of the version to be published; and (d) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Specifically, all authors were involved with the following: (a) conceptualization; (b) writing (original draft); and (c) writing (review and editing).

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