TITLE: Studying the neuropsychological sequelae of SARS-CoV-2: lessons learned from 35 years of neuroHIV research

Andrew Levine, Ph.D.*

Department of Neurology

David Geffen School of Medicine

University of California, Los Angeles

Ned Sacktor, M.D.

Department of Neurology

Johns Hopkins University School of Medicine

James T. Becker, Ph.D.

Departments of Psychiatry, Neurology, and Psychology

University of Pittsburgh

*Corresponding Author: Reed Neurological Research Building

710 Westwood Plaza, Room 3-234

Los Angeles, CA 90095

ajlevine@mednet.ucla.edu

(P) 562-477-5963

(F) 510-280-2993

Abstract

The virology of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the human immune response to the virus are under vigorous investigation. There are now several reports describing neurological symptoms in individuals who develop coronavirus disease 2019 (COVID-19), the syndrome associated with SARS-CoV-2 infection. The prevalence, incidence, and clinical course of these symptoms will become clearer in coming months and years through epidemiological studies. However, the long-term neurological and cognitive consequence of SARS-CoV-2 infection will remain conjectural for some time, and will likely require the creation of cohort studies that include uninfected individuals. Considering the early evidence for neurological involvement in COVID-19, as well as the known albeit less severe neuroinvasiveness and neurovirulence of other human coronaviruses, it may prove helpful to compare SARS-CoV-2 to another endemic and neurovirulent virus, Human Immunodeficiency Virus-1 (HIV-1), when designing such cohort studies and when making predictions about neuropsychological outcomes. In this paper, similarities and differences between SARS-CoV-2 and HIV-1 are reviewed, including routes of neuroinvasion, putative mechanisms of neurovirulance, and factors involved in possible long-term neuropsychological sequelae. Application of the knowledge gained from over three decades of neuroHIV research are discussed, with a focus on alerting researchers and clinicians to the challenges in determining the cause of neurocognitive deficits among long-term survivors.

Key Words: Neuropsychology, COVID-19, SARS-CoV-2, neuroHIV, HIV-associated neurocognitive disorders

COVID-19 – Neurological Symptoms and Outcomes

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated syndrome, coronavirus disease 2019 (COVID-19), first gained attention in December of 2019 in the city of Wuhan, China(1). Transmission to humans was zoonotic, apparently originating in bats(2), possibly via pangolins(3) and/or snakes(4). Herein we use the terms SARS-CoV-2 and COVID-19 to describe the virus and its associated clinical syndrome, respectively.

All studies of neurological outcomes have occurred in individuals diagnosed with COVID-19 and have consisted of case reports and case series. There are, as of yet, no studies of the neuropsychological sequelae of SARS-CoV-2 infection or COVID-19 illness, although helpful speculative articles have been published(5) and others are forthcoming. The largest published study of neurological symptoms in laboratory-confirmed SARS-CoV-2 infected cases comes from Wuhan, China(6). In that case series, 36.4% of 214 patients developed neurological symptoms that included headache, dizziness, and (less commonly) mental status change and paresthesia. It is important to point out that 41% of the sample from the study had severe illness, and it was the more severely affected patients who exhibited the neurological symptoms, suggesting that neurological symptoms could have been related to systemic factors or exacerbation of pre-existing medical conditions. In another case series of 58 COVID-19 patients (median age 63-years) admitted to a French hospital due to acute respiratory distress syndrome (ARDS), 84% had neurological symptoms at some point during their hospitalization, 14% of whom presented with neurological symptoms upon admission(7). Corticospinal tract symptoms were observed in 67%, and 36% had dysexecutive syndrome (e.g., inattention and disorientation). Of those who underwent magnetic resonance imaging (MRI) of the brain, 62% had leptomeningeal enhancement and 23% had cerebral ischemic stroke. All eleven patients who underwent perfusion imaging had bilateral frontotemporal hypoperfusion; however, only

one of eight patients who received EEG testing had non-specific abnormal findings. It is unclear whether the patients with known pre-existing neurological disorders were among those showing symptoms. A study of 43 COVID-19 patients in England(8) revealed five major categories of neurological involvement: (i) encephalopathies (n = 10), (ii) inflammatory CNS syndromes (n = 12), (iii) ischemic strokes (n = 8), (iv) peripheral neurological disorders (n = 8) primarily consisting of Guillain-Barré syndrome, and (v) patients with CNS disorders who did not fit into these categories (n = 5). Finally, it is notable that other case series have not reported a significant incidence of neurological symptoms. For example, among 41 COVID-19 patients in China, only headaches were reported among 8% of the sample(9). Also, two larger case series currently in pre-print, one of 20,662 patients in China(10) and the other of 1000 patients in New York City(11), do not describe prominent neurological symptoms, with the possible exception of headache. Whether these discrepant findings are due true differences in the populations or the syndromes described, or to a lack of standardized data and/or symptom collection methods is unclear.

Hyposmia/anosmia and hypogeusia/dysgeusia have received significant media attention. Such symptoms were reported in the first case series described above(6) and in a case series from Italy(12). Whether or not these symptoms are truly neurological in nature is uncertain at this time. For example, a case study from France indicated that bilateral obstructive inflammation of olfactory clefts impaired olfactory function by preventing odorant molecules from reaching the olfactory epithelium(13), suggesting that loss of smell or taste may not have a neurological cause, at least not in all cases. Conversely, while anosmia is known to occur in many upper respiratory tract infections, many patients with COVID-19 lose smell despite absence of congestion(14).

Studying of the Neuropsychology of SARS-CoV-2

A steady stream of case reports have described severe acute neurologic conditions in a minority of COVID-19 patients, some of whom were relatively young. One such study from Japan described a 24-year old man who developed meningitis and encephalitis. MRI findings from that case included hyperintensity along the wall of right lateral ventricle and hyperintense signal changes in the right mesial temporal lobe and hippocampus(15). Another case report described acute necrotizing hemorrhagic encephalopathy in a 50+ year old, female with laboratory-verified COVID-19(16). Head CT revealed symmetric hypoattenuation within the medial thalamic nuclei bilaterally, whereas brain MRI revealed hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. Her pre-morbid medical history was not described. Five younger (<50 years old) patients presented with large-vessel stroke within a two-week period at a New York City hospital, where historically an average of only 0.73 patients under 50 were treated for the condition during the same timeframe over the previous 12 months(17). A similar case series, describing six patients with stroke under the age of 55, was recently reported from Iran(18).

In summary, these early case reports suggest that a minority of COVID-19 cases have neurological symptoms ranging in severity from very mild (e.g., headache and loss of smell/taste) to severe (e.g., encephalitis), and that symptoms can occur before or after other "core" symptoms of COVID-19 (6). However, the meaning of these observations is unclear, as the studies described above did not include control groups consisting of uninfected patients with similarly severe respiratory or other symptoms, or those who had undergone similar medical procedures (e.g., ventilation and sedation) for other conditions. Additionally, it is unclear if the discrepancy of findings in case series is due to differences in data collection methods, and whether the patients described in the aforementioned studies were tested for other potentially

neuroinvasive viruses that can lead to similar neurological conditions as those reported for COVID-19, such as influenza A (19-21).

Potential Mechanisms of Central Nervous System Involvement in SARS-CoV-2 Infection

Previously identified human coronaviruses (HCoV) are neuroinvasive and, as the evidence reviewed below suggests, neurovirulent. Initial evidence suggests that SARS-CoV-2 is also neuroinvasive, although its neurovirulance will take some time to determine. Below, we review discuss potential acute and long-term neurological and neuropsychological sequelae due to direct and indirect routes of pathogenicity. Other reviews are also avaibable(22).

Direct Causes

The aforementioned cases studies suggest that SARS-CoV-2 is both neuroinvasive and neurovirulent. Furthermore, research findings of other viruses, including HCoVs, raise the possibility that it may persist in the central nervous system (CNS) following systemic clearance. As described in a recent review, coronaviruses can enter the CNS via two routes(23). The first is the hematogenous route, in which HCoVs enter the circulatory system via the human airway epithelium(24) and then infect epithelial cells of blood-brain barrier (BBB) or blood-cerebrospinal fluid barrier in the choroid plexus. HCoVs can also infect myeloid cells, which then shuttle it into CNS(25-27), a route favored by HIV-1(28-31). In both cases, HCoVs enter the cells by first binding to a the ACE2 receptor, after which they enter endosomes and fuse the viral and lysosomal membranes(32). The second is the neuronal retrograde route, in which viruses exploit periphery nerves and axonal transport mechanisms to gain entry to CNS(33, 34). This could occur via several possible cranial nerves, including olfactory(35), trigeminal(36, 37), and vagus nerves(38, 39). HCoV-OC43, a coronavirus that infects humans and cattle with generally mild symptoms, uses this neuron-to-neuron route(40). In addition, both SARS-CoV-1 and the

Middle East respiratory syndrome conoravirus (MERS-CoV) can also gain access to the CNS via peripheral nerve terminals and subsequent synapse-connected pathways(41-43). In transgenic mice, MERS-CoV then spreads to the brainstem, thalamus, and other brain regions(44). There is evidence that SARS-CoV-2 also has the potential to be neuroinvasive. SARS-CoV-2 enters angiotensin-converting enzyme 2 (ACE2)-expressing cells, which are found in airway epithelia, lungs, vascular endothelia, kidney, and small intestine(45). ACE2 is also expressed in the mouse and rat brain, in particular the brainstem regions that control cardiovascular functioning(46, 47), suggesting a direct role of the virus in ARDS(45).

While most, if not all HCoVs are neuroinvasive, only some appear neurovirulent(44, 48, 49). SARS-CoV-1, HCoV-OC43, and HCoV-229E (a coronavirus that infects bats and humans, with generally mild symptoms to the latter) are known to be neurotropic in humans(50-52). SARS-CoV-1 causes neuronal death in the absence of encephalitis in human ACE2 transgenic mice(53), and neuropathological findings from humans who died of SARS, the syndrome caused by SARS-CoV-1, included cerebral edema, meningeal vasodilation, ischemic changes of neurons, and demyelination(25, 50, 53). HCoV-OC43 infection of mouse CNS induces glutamate excitotoxicity with subsequent neuronal damage and disruption of glutamate homeostasis, with the downstream effect being limb paralysis and possible demyelination(23). HCoV-OC43 has also been linked to encephalitis in humans(54). Evidence that MERS-CoV is neurovirulent includes case reports of psychosis and seizures(55), as well as mental status changes, paralysis, ischemic stroke, Guillian-Barre syndrome, and neuropathy that arise 2-3 weeks after resolution of respiratory symptoms (56).

When assessing the possible neurovirulence of SARS-CoV-2, one could consider genetic similarities with other HCoVs. SARS-CoV-2 and SARS-CoV-1 are 79% genetically

homologous(57). A mutation in a gene that produces SARS-CoV-2 spike protein gives the virus an affinity for ACE2 that is at least 10x greater than SARS-CoV-1(58), likely explaining in part the former's greater infectivity. During the 2002-2003 SARS outbreak, a variety of neurological conditions appeared 3-4 weeks into the course of the illness in a small number of patients, including polyneuropathy, encephalitis, and aortic ischemic stroke(59). This seems to differ from SARS-CoV-2, in which some neurological symptoms appear earlier in the course of illness(6). Whether this is due to the difference in ACE2 affinity or other functional differences will be the subject of future studies. Infection with the Middle East Respiratory Syndrome (MERS) coronavirus (MERS-CoV) led to the most deadly syndrome in 2012. As with SARS-CoV-1 and 2, MERS-CoV originated in bats(60), with the dromedary serving as the vector to humans. However, it is only 50% genetically homologous to SARS-CoV-2(57).

Finally, the chronic presence of SARS-CoV-2 in the brain could conceivably result in long-term neurological and neuropsychological sequelae. Several other viruses exert chronic deleterious effects in human CNS. The most well studied example is HIV-1 infection, as discussed in detail below. Other examples include human herpes viruses, which have been associated with later risk of Alzheimer's disease, multiple sclerosis (MS), and other neurodegenerative disorders(61-64), and Influenza A which is associated with later risk for Parkinson's disease(65). The long-term persistence of HCoVs in the CNS, and their potential to cause delayed neurologic dysfunction(52, 66-70), may be underestimated. Several studies report putative links between HCoV in the human neurologic disorders, including encephalitis(54), multiple sclerosis(66, 68), Parkinson's disease(67), and acute demyelinating encephalomyelitis(71). Both HCoV-229E and HCoV-OC43 have been found in brains of deceased MS patients MS(49, 51, 69, 72) and those who had encephalomyelitis (71, 73). However, it is important to consider that the high prevalence of some HCoVs in human tissue makes it difficult to interpret such findings(74).

Indirect Causes

Even without considering its potential for neurovirulence, SARS-CoV-2 infection may lead to poor neurological outcomes via indirect routes. There have been recent reports in the media about high stroke rates in relatively young patients being treated for COVID-19, but published findings are scant. A case series described three COVID-19 patients aged 65-70 in Wuhan, China who developed coagulopathy and antiphospholipid antibodies with subsequent multiple cerebral infarcts damaging a wide range of brain regions(75). All had history of hypertension and other medical illnesses. In addition, the reported elevated levels of D-dimer and suppressed levels of platelets(76) may make patients with severe COVID-19 more prone to cerebrovascular accidents. Those patients who develop acute respiratory distress syndrome (ARDS) are at risk of cerebral hypoxemia(77). Many of those with ARDS are intubated and treated with mechanical ventilators, a procedure with substantial risks(78). Indeed, a case series of eighteen deceased COVID-19 patients aged 53-75 who underwent neuropathological examination revealed only signs of hypoxia in brain tissue(79). Eleven had received mechanical ventilation before death. Also notable is that virus was detected at low levels in only five patients.

The reported “cytokine storms” reported in severe COVID-19 cases(80) can lead to multiple organ damage, leading to renal and hepatic liver dysfunction and cardiac dysfunction (81), all of which can have adverse effects of cognitive functioning(82-84). Indeed, this acute inflammatory state can also lead to CNS damage(85). Whether or not cytokine-driven neuroinflammation might also be present in infected individuals with more mild symptoms might also be considered in future studies. Finally, some have proposed that CNS-related autoimmune disorders could arise post-SARS-CoV-2 infection(86) via “molecular mimicry”(87), as has been reported in SARS-CoV-1 and MERS-CoV infection(56, 59).

In summary, there is ample evidence from COVID-19 case reports and studies of other HCoVs that SARS-CoV-2 is both neuroinvasive and neurovirulent, possibly via different routes. Furthermore, poor neurological outcomes can result from indirect causes linked to systemic infection and aggressive treatment of COVID-19,which is similar to HIV-1.

HIV-1: Summary of Neurological and Neuropsychological Symptoms and Sequelae

A dementia syndrome associated the HIV-1 was first systematically described and termed AIDS Dementia Complex in 1986 (88). For the next 10 years, the prevalence of what came to be more commonly referred to as HIV-Associated Dementia was about 16%(89) and typically indicated advanced immune dysfunction and a poor prognosis. After combined or highly active antiretroviral therapy (cART or HAART) became widely available in 1996, the prevalence of HIV-Associated Dementia dropped to less than 5%(90-92). However, a more chronic and less severe form of cognitive impairment become evident, leading to updated research criteria published in 2007 that captures the full spectrum of neuropsychological deficits thought to be due to HIV (93). The term for this broad classification that captures the full severity range of cognitive impairment, from mild deficits without noticeable impact on day-to-day functioning to debilitating dementia, is HIV-Associated Neurocognitive Disorders, or HAND. The nature of cognitive deficits varies widely and has also changed over time as HIV-1 infection has become more chronic in nature(94). Estimates of the current prevalence of HAND vary considerably, with between 15-84% of infected individuals meeting criteria at any one time (94-99). The majority of HAND diagnoses are mild, termed asymptomatic neurocognitive impairment (ANI) according to current research criteria(93). However, the inclusion of ANI in current diagnostic schema may have had the unintended consequence of high rates of false positive diagnoses due to the low threshold for cognitive impairment, thereby inflating HAND prevalence

estimates(100, 101). Indeed, a significant percentage of healthy HIV-uninfected individuals with no known neurologic or psychiatric illness would meet criteria for ANI, save for the fact that they are not HIV-infected(101-105). Indeed, two recent studies have attempted to deal with the problem of high false discovery rates using the method of multivariate normative comparison(106, 107). In both studies, the rate of cognitive impairment among HIV-infected individuals was almost identical to that of uninfected individuals, demonstrating that empirically-defined thresholds for impairment may be a more reliable method.

Both in the pre-cART and current era (i.e., since 1996), HIV encephalitis (HIVE) is considered to be a major neuropathological basis of HIV-associated dementia(89, 108-117). However, the vast majority of HAND cases present with milder symptoms(118, 119) and do not have neuropathological findings consistent with HIVE(120). Accumulating evidence suggests that for the vast majority of HAND cases that are mild-to-moderate in severity, cognitive impairment is due largely to synaptodendtric dysfunction driven by chronic CNS inflammation(109, 111, 117, 120-124). As with the direct and indirect mechanisms of CNS damage proposed for SARS-CoV-2 described above, the neuropathogenesis of HAND likely has direct and indirect routes. In the direct route, HIV-1 in brain macrophages and other cells release viral proteins that harm nearby neurons and other cells (109, 117, 125-128), and cross-talk between neurons and microglia can also drive synaptodendritic dysfunction(129). In the indirect route, macrophage proliferation, microglial activation, astroglial activation, and dysregulated cytokine expression and production (109-117) drive inflammation, resulting in synaptodendritic dysfunction. Indeed, increased migration across the blood-brain barrier of monocytes (130, 131) driven both by chemokine gradients originating in the CNS and from a peripheral immune response (117, 132, 133) is thought to be a major factor underlying HAND(134).

SARS-CoV-2 and HIV-1: Differences in Virology and Host Immune Response

The virology of HIV-1 differs substantially from coronaviruses such as SARS-CoV-2. HIV-1 is a retrovirus whose RNA genome is reverse transcribed into double-stranded DNA and integrated into the cellular DNA, where it can remain hidden from the host's immune surveillance in a latent state for 8-10 years, during which time the host remains symptom free (135). Once activated, the integrated HIV-1 DNA uses the host's replication mechanisms to create additional RNA genomes and viral proteins, which then exit the cell to propagate the infection, much as other viruses including HCoVs.

HIV-1 targets cells of the immune system, specifically CD4+ helper T cells(136), monocytes(125), macrophages(125), and dendritic cells(137) via binding to CD4 receptor and CCR5 co-receptor, although some strains use CXCR4 as the co-receptors for viral entry (138, 139). The body's adaptive immunity defenses are largely ineffective against HIV-1. Cell-mediated immunity driven by T-cells is largely disabled because of the virus's predilection for those cells(136). Furthermore, antibodies produced by B-cells are not effective against HIV-1. As such, without treatment with a combination of antiretroviral medications the host becomes vulnerable to opportunistic infections and the eventual development of Acquired Immunodeficiency Syndrome (AIDS). Virus-harboring macrophages move via chemotaxis to seed other body regions with the virus, including the CNS(117, 132, 133) that serves as a sanctuary for the virus. In the CNS, HIV-1 is largely safe from immunosurveillance, infecting microglia which serve as a primary reservoir of the virus(140). In the case of SARS-CoV-2, the virus binds to the spike protein on the surface of epithelial cells, enters endosomes, is then dispersed into the cytoplasm when the viral and lysosomal membranes fuse (32). It is unclear whether SARS-CoV-2 will also be able to persist in the brain. One proposed mechanism linking other HCoV infections with later neurologic disease is chronic infection of oligodendrocytes and

glial cells(52, 141), perhaps due to the lower immunosurveillance in the brain that makes it a sanctuary for HIV-1. If this is also the case for SARS-CoV-2, our current understanding of antiviral medication penetrance into the CNS(142), as well as innovative methods to eradicate viruses from the brain(143), will be useful.

That HIV-1 is a retrovirus, along with its high mutation rate, makes it almost impossible to eradicate from host cells. Only two individuals are known to have been completely cleared of HIV-1 following allogeneic haemopoietic stem-cell transplantation from a donor homozygous for the delta-32 allele on the CCR5 gene(144, 145). While there is no evidence of HIV-1 RNA in cerebrospinal fluid, it remains unknown whether HIV-1 persists in the brains of these individuals, who are still living.

It remains uncertain if lasting adaptive immunity to SARS-CoV-2 will be possible. Based on human immune response to other coronaviruses, at least temporary immunity is expected and illness from later infections may be less severe(146). As with HIV-1, infectability and the host immune response may vary according to host genotype, although further study is required to validate these findings(147). For example, mutations in the ACE2 gene could conceivably influence infectivity and symptom type/severity. In the case of HIV-1, discovering that the CCR5 was a co-receptor(148) led to the development of a new class of antiviral medication(149). However, the application of host genetics to HAND has been less successful(150), possibly owing to poor diagnostic reliability(151).

Finally, in regards to maladaptive immune responses, the “cytokine storms” described in COVID-19 patients that is responsible for severe organ damage and mortality are sometimes seen during the acute phase of HIV-1 infection, but in a less severe form(152). However, upon

initiation of antiviral therapy, a minority of HIV-infected patients can develop immune reconstitution inflammatory syndrome (153), which can result in significant morbidity and even death.

In summary, while there are fundamental differences in the virological and immune response to SARS-CoV-2 and HIV-1, their shared potential for CNS persistence and neurovirulence could make current knowledge of neuroHIV helpful for devising treatments and designing studies of the neuropsychological consequences of SARS-CoV-2 infection.

Considering Long-Term Neuropsychological Outcomes in SARS-CoV-2 Infection: Why Comorbidities Matter

Assuming SARS-CoV-2 like other HCoVs can have a lasting presence in the CNS(49, 51, 52, 69, 72), its potential to provoke a chronic neuroinflammatory immune response similar to HIV-1 should be considered in the pathogenesis of neuropsychological deficits. Furthermore, long term tracking of survivors will determine whether CNS exposure to the virus increases risk of later neurodegenerative illness(52, 56, 59, 66-70, 86, 87). In addition, based on findings from over 30 years of neuroHIV research, it is just as important to consider the various comorbidities and other factors that are more likely to affect neuropsychological functioning.

The prevalence of HAND may be overestimated. Large case-control studies consisting of only HIV+ participants(91, 93, 154, 155) or those that included mismatched HIV- participants(94) generally point to the virus itself as the primary cause of neurocognitive and neurophysiological aberrations. However, cohort studies that include well-matched HIV-uninfected control participants indicate that, at least in generally cART-treated individuals, it is primarily medical and psychiatric comorbidities that underlie neurocognitive impairment(156, 157), with a smaller

percentage of neurocognitively impaired cases apparently due to HIV infection. Similarly, neurophysiological changes in those with HIV, as determined through magnetic resonance imaging, appear due largely to medical comorbidities, including hypertension, diabetes mellitus, higher body mass index, and elevated visceral fat(158, 159). It is interesting to note that age-related medical comorbidities are more prevalent in the context of HIV(160-165), possibly due to accelerated biological aging caused by the retrovirus(166-168). As described in the opening section, case studies to date point to indirect, medical-related causes for neuropsychological deficits in COVID-19 survivors, including cerebrovascular pathologies (75, 76), cerebral hyoxemia(77), and chronic illnesses resulting from organ damage cause by acute cytokine dysregulation(81-85). In addition, that COVID-19 presents as more severe in older individuals and those with medical conditions that are also risk factors for cognitive impairment will further complicate the clinical picture. More specifically, hypertension, diabetes, cancer, cardiovascular disease, and chronic respiratory illness are risk factors for severe COVID-19 and/or death(169), and also for neuropsychological deficits(82, 170-175). In addition, some have posited that ACE2 inhibitors used to treat hypertension and diabetes may increase the expression of ACE2, making cells more vulnerable to SARS-CoV-2 infection and, as a consequence, making those individuals more prone to severe COVID-19(176). Therefore, determination of later neuropsychological impairment in survivors of SARS-CoV-2 infection and COVID-19 illness will require consideration of these and other medical comorbidities.

Not surprisingly, HIV-1 infection is associated with greater risk of psychiatric illness, and this can exacerbate and complicate cognitive impairment (177-180). Depression can result from the personal and psychosocial impact of the disease, as well as biological effects of infection and treatment(181). Considering the relatively high fatality rate among individuals who become infected with SARS-CoV-2, as well as the emotional and financial devastation caused by the

pandemic, psychological disorders such as post-traumatic stress disorder (PTSD) and depression should to be considered as primary diagnoses and contributing factors to neurocognitive impairment(86). Indeed, early indications suggest higher prevalence of anxiety disorders such as PTSD stemming from either surviving infection with SARS-CoV-2 or serving as a front-line healthcare worker(182), as well as those living near the epicenter of the outbreak(183). This appears consistent with studies from the 2003 SARS and 2005 MERS outbreaks, which reported high rates of PTSD(184-187). The impact of death due to COVID-19 may also have a more profound impact on loved ones. In fact, one very important difference between COVID-19 and HIV-1 infection is that in the terminal stages of the latter, a patient's family member or close friend are able to be bedside to express final thoughts of love and comfort. However, with COVID-19 this is not the case, as loved ones have been prohibited from accompanying terminally ill patients because of the extremely high risk of infection via respiratory droplets.

Finally, in order to accurately delineate long-term neuropsychological outcomes of SARS-CoV-2 infection, cognitive testing of individuals with active symptoms (i.e., COVID-19) should be avoided, as studies have shown that even very mild upper respiratory viral infections can have acute effects on neuropsychological functioning(188, 189).

Approaches for Studying the Neuropsychological Sequelae of SARS-CoV-2 infection

In order to characterize the long-term neuropsychological sequelae of SARS-CoV-2 infection and/or COVID-19, large and diverse cohort studies that include both infected (historically or actively) and never-infected individuals will be required. Such studies will allow for longitudinal characterization of cognitive functioning while considering comorbidities and other potential factors affecting such functioning (e.g., medication type, psychiatric and medical comorbidities).

Such cohort studies will also likely to capture a substantial number of seroconverters (i.e., those who become infected during their study participation). Large cohorts studies of HIV-1, such as the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study, have contributed significantly to the understanding of the natural and treated history of HIV-1 infection, including neuropsychological outcomes with consideration of medical and other comorbidities(156, 190-195) but have been limited to domestic participants.

Drawing from the history of neuroHIV research, in which the western research community either did not recognize or failed to appreciate until the mid-2000s that HIV-associated neurocognitive impairment was a global problem particularly in resource-limited countries(196, 197), we believe that it is critical to examine the neuroepidemiology of SARS-CoV-2 in resource-limited countries as soon as possible. Because of the respiratory mode of transmission of SARS-CoV-2 and limitations in personal protective equipment and medical supplies in hospitals in resource-limited countries, it is likely that infection rates will be in much higher number. In particular, Latin America, where standard public health policies to counter the pandemic are often being ignored by local government officials or even top leaders (e.g., Brazil), and sub-Saharan Africa, in which the majority of residents live in densely populated communities where social distancing is not possible, are two areas that are particularly susceptible to rampant SARS-CoV-2 infection. Preventing the spread of infection requires basic resources like those to permit frequent handwashing (i.e., clean water and soap) and social distancing (e.g., adequate housing). Establishment of international cohorts will also allow for the delineation of genetic, environmental, and cultural factors involved in neuropsychological outcomes of SARS-CoV-2 infection.

Domestically, cohorts must include a broad cross-section of races, over-sampling (proportionally) for African-Americans and Latinos, while maintaining an equal representation of men and women across all groups. In addition, the samples must also represent a range of socio-economic strata, so as not to conflate “race” with other social factors. Finally, appropriate at-risk individuals must be included – that is individuals who based on occupation, life-style, or other factors may be at greater risk for infection than the population as a whole.

Perhaps drawing from the experiences with HIV-1 and other pandemic viruses, and recognizing that early action will beget stronger prevention and intervention, the National Institutes of Health and other public and private funding sources have already begun soliciting grant applications that leverage the infrastructure of extant cohort studies, including those of HIV-1, which will more quickly generate epidemiological data that can effectively shape public health policy and pharmaceutical development efforts. This approach will also generate important data concerning HIV-1/SARS-CoV-2 co-infection.

Conclusion

The SARS-CoV-2 pandemic is like nothing the world has seen in modern times. However, thanks to modern technology and scientific thinking, elucidating host susceptibility factors (e.g., genetic, medical, psychosocial) and tracking the long-term effects of the virus and its associated syndrome is already being implemented or planned. Thinking ahead, long-term monitoring of SARS-CoV-2 antibody positive individuals and uninfected controls in cohort studies are required to determine if the COVID-19 and/or asymptomatic infection has later effects on neuropsychological functioning while also considering potential mediating or contributing factors, as has been done with HIV-1(156, 195, 198-200). Thus, drawing from lessons learned from over three decades of domestic neuroHIV research, as well as more recent international

research, the scientific community will be better prepared to effectively design and execute such studies, as well as interpret their findings.

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