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HIV and COVID-19: two pandemics with significant (but different) central nervous system complications

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Abstract

Human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cause significant neurologic disease. Central nervous system (CNS) involvement of HIV has been extensively studied, with well-documented invasion of HIV into the brain in the initial stage of infection, while the acute effects of SARS-CoV-2 in the brain are unclear. Neuropathologic features of active HIV infection in the brain are well characterized whereas neuropathologic findings in acute COVID-19 are largely non-specific. On the other hand, neuropathologic substrates of chronic dysfunction in both infections, as HIV-associated neurocognitive disorders (HAND) and post-COVID conditions (PCC)/long COVID are unknown. Thus far, neuropathologic studies on patients with HAND in the era of combined antiretroviral therapy have been inconclusive, and autopsy studies on patients diagnosed with PCC have yet to be published. Further longitudinal, multidisciplinary studies on patients with HAND and PCC and neuropathologic studies in comparison to controls are warranted to help elucidate the mechanisms of CNS dysfunction in both conditions.

Keywords: HIV, COVID-19, HIV-associated neurocognitive disorders, Long COVID, Post-COVID conditions, Neuropathology

Introduction

Human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are both human viruses that cause neurologic disease. HIV is a retrovirus and is clearly neurotropic, with tropism for microglial cells in the central nervous system (CNS), infection of which generates downstream effects that injure brain parenchyma. Its clinical and pathologic manifestations are fairly well characterized. By contrast, coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 leads to neuropsychiatric morbidity in a significant percentage of infected patients, but the mechanisms for this are heterogeneous and may include indirect effects on the brain through activation of inflammatory cascades, possible microangiopathic changes and disruption of the neurovascular unit. However, knowledge of HIV neuropathogenesis may be instructive for understanding many aspects of COVID-19 neuropathogenesis. The Brain Research Institute at UCLA sponsored two half-day “Neurovirology Affinity Group” meetings in the spring of 2022 and 2023 at which a multidisciplinary team of representatives from neuropathology,

cardiovascular pathology, microbiology, radiology, infectious disease, cardiology, neurology, and psychiatry convened to address the CNS complications of COVID-19, considering what we have learned from the HIV pandemic over the past several decades. The meeting aims were to identify gaps in current knowledge on CNS disease in COVID-19 and HIV and potential directions for future study. This selective review summarizes the main topics discussed and conclusions reached.

Human immunodeficiency virus (HIV)

An immunodeficiency disease, later named acquired immunodeficiency syndrome (AIDS), started to become recognized in the summer of 1981 in the United States [1,2]. This discovery was followed soon after by the identification of human immunodeficiency virus-1 (HIV-1) as the causative agent [3–5]. At the time, nearly all patients infected with HIV progressed to end stage AIDS with fatal opportunistic infections and malignancies, many involving the CNS [6]. A few years later, HIV-2, primarily restricted to West Africa, was discovered [7–9]. With the advent of combined antiretroviral therapy

(cART) in the mid 1990s, HIV has become a chronic disease with near normal life expectancies, at least in industrialized countries [6,10]. There have been approximately 40 million deaths since the beginning of the pandemic and currently 38 million infected worldwide according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) [11].

HIV-1 and HIV-2 are lentiviruses of the retrovirus family and predominantly infect monocytes/macrophages, as with all lentiviruses, but also CD4 T-cells by binding to CD4 and the chemokine co-receptors CXCR4 and CCR5 [12,13]. Other co-receptors such as CCR2 and CCR3 have also been reported to mediate infection *in vitro* [12,13]. Infection of macrophages (and microglia) is primarily through CCR5 [14,15]. The entrance of virus into the cell may result in productive infection or latent infection [7,12,16,17]. HIV is neuroinvasive, characteristic of lentiviruses, and enters the CNS at the initial stage of infection [13,18–20].

Neurologic manifestations

HIV causes neurologic complications, due to opportunistic infections and HIV infection itself, in over half of patients not receiving cART [21,22]. With the advent of cART, the rates of opportunistic infections of the CNS such as by cytomegalovirus, toxoplasma, cryptococcus and progressive multifocal leukoencephalopathy caused by JC virus, as well as primary CNS lymphoma, have decreased in some series [21,23]. HIV-associated neurocognitive disorders (HAND), with revised consensus nomenclature and criteria in 2007 [24], previously referred to as AIDS dementia complex and HIV-1 associated cognitive/motor complex [25–28], comprise a spectrum of cognitive dysfunction associated with HIV infection [24,25]. HAND includes, with increasing severity, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD), and continues to affect approximately 33–50% of treated HIV-positive individuals [24,29–31]. HAD is the most severe and was the most common form of HAND in the pre-cART era but has decreased with the advent of cART, now comprising less than 10% of those with HAND [6]. However, the overall proportion of individuals with HAND has not changed in the cART era due to a

relative increase in the milder forms of HAND, the pathogenesis and neuropathologic substrates of which are unclear [6,31].

The clinical features of HAND have also changed before and after cART [32]. In the pre-cART era, patients commonly presented with extrapyramidal signs (bradykinesia, rigidity and tremor) and more frequent subcortical features with motor dysfunction and speed of processing deficits [26,32–35]. In the cART era, extrapyramidal signs are less common with more cortical features with deficits in learning, memory and executive functioning [32–34,36]. Risk factors for HAND include older age [37], cerebrovascular disease risk factors [38,39], duration of HIV infection and history of AIDS defining illness [40], lower CD4 nadir [40,41], and in treatment naïve patients, burden of HIV DNA in monocyte-enriched peripheral blood cells [42]. Currently, the only treatment for HAND is cART, but cART is effective in only a subset of patients with HAND [32,43]. After the advent of cART, the median survival of HAD patients increased to 38 months compared to 5 months pre-cART [44], and most individuals with HAND on cART remained stable [29,32]. However, even in patients on cART, HAND is associated with shorter survival and is an important cause of morbidity and mortality in the aging HIV-positive population [45–47]. A recent study showed that cognitive decline in HIV positive individuals was not associated with age or markers of HIV disease but rather comorbidities such as hypertension and diabetes [48].

Before cART, brain magnetic resonance imaging (MRI) studies showed accelerated global white matter atrophy and cerebrospinal fluid (CSF) volume increase (corresponding to tissue loss) as well as atrophy of the caudate in HIV-positive individuals [49,50]. Postmortem MRI studies demonstrated that increase in volume of abnormal white matter and decrease in volume of deep gray matter correlated with increasing viral burden as assessed by immunohistochemistry for HIV protein [51]. Even after cART, compared to HIV-negative individuals, HIV-positive individuals show higher rates of white matter atrophy, which correlate with lower CD4 counts [52]. MRI changes can be seen in all degrees of HAND, with individuals with HAND showing greater abnormality in cerebral white matter compared to

neurocognitively intact HIV-positive individuals [53]. Utilizing dynamic contrast enhanced perfusion (DCE-P) MRI, a marker of capillary permeability, to assess for blood-brain barrier (BBB) disruption, Chaganti et al. showed impaired BBB in the frontal white matter and basal ganglia in virally suppressed patients with HAND compared to controls [54].

Neuropathologic findings

Neuropathologic studies have made important contributions to understanding HIV infection in the CNS [7,12,55–57]. HIV has been isolated from the CSF, brain including frontal and temporal lobes, caudate, and cerebellum, spinal cord, and sural nerve from AIDS patients with meningitis, encephalopathy, myelopathy, and peripheral neuropathy [58–60]. Even in asymptomatic patients, HIV specific antibodies can be detected and HIV isolated from the CSF [19,61]. HIV-1 has also been isolated from the brain 15 days after a patient accidentally inoculated himself with HIV-1 infected white blood cells [62]. HIV is thought to enter the CNS predominantly through a Trojan horse-like mechanism in which HIV-1 infected monocytes cross the blood-brain barrier (BBB) and release viral particles in the brain parenchyma [16,19,63] although entry may also be facilitated through a disrupted BBB [64]. HIV-1 has been shown to productively infect brain microglia/macrophages [65–69]. Although HIV-1 DNA and proteins have been detected in other CNS cell types, such as astrocytes and endothelial cells in postmortem brain [17,18,70,71] and shown to infect other cell types in vitro, their role in propagation of CNS infection is unclear [12].

Neuropathologic changes can be seen early in HIV infection [20,72]. In asymptomatic HIV-positive patients who died from other causes, lymphocytic leptomeningitis, perivascular mononuclear cell infiltrates, microgliosis and astrocytic gliosis, which is more prominent in white matter compared to gray matter, myelin pallor, and elevated cytokines, have been seen along with HIV-1 proviral DNA (but no HIV-1 protein) in a subset [20,72,73]. Before the advent of cART, most HIV-positive individuals progressed to AIDS [6], and the majority 70–90 % demonstrated neuropathologic abnormalities at

autopsy [27,55,56,68,74–77]. In addition to frequent opportunistic infections and lymphomas seen in the context of immunodeficiency, there are characteristic neuropathologic findings attributed to HIV infection itself [19,27,68,74]. These were summarized in consensus guidelines in 1991 [28] and include HIV encephalitis (HIVE), HIV leukoencephalopathy, lymphocytic (aseptic) leptomeningitis, and diffuse microgliosis and astrogliosis in cerebral gray matter (“diffuse poliodystrophy”) [7,56,78]. HIV encephalitis, seen in 10–63 % of autopsies, is characterized by microglial nodules and multinucleated giant cells (Figure 1) and/or evidence of HIV in the brain [57,79,80] typically affecting the white matter most severely, followed by the deep gray matter and then cortex [27,28,65,80]. Multinucleated giant cells, often seen in a perivascular distribution and more commonly in the subcortical white matter or deep gray matter, are the hallmark finding in HIVE and result from virus-induced fusion of macrophages which have been shown to contain HIV protein [65,81–83].

In the post cART era, the majority of HIV positive individuals show no HIV related neuropathology at autopsy, although HIVE has been reported in 8–25 % of case series with equal or even increased frequency post cART in some series [84–87]. Opportunistic infections, albeit decreased in frequency after cART, are still seen [84–92]. HIVE indicates active viral replication and is an important pathologic substrate of HAD [93], but not all subjects with cognitive impairment have HIVE and not all patients with HIVE have cognitive impairment, which was seen before but especially after the advent of cART [56,68,81,84,88,94]. In the post cART era, HIV associated neuropathologic findings have not correlated with cognitive impairment [84].

AIDS patients demonstrate cortical atrophy and neuronal apoptosis [95,96], but neither neuronal apoptosis [97] nor neuronal loss in the frontal and temporal cortices of patients with AIDS [98] correlate with dementia. On the other hand, decreased cortical synaptic density and dendritic complexity were demonstrated even with mild cognitive impairment and have been shown to correlate with severity of cognitive impairment [99–101]. Disruption of the BBB has been seen in patients both with AIDS

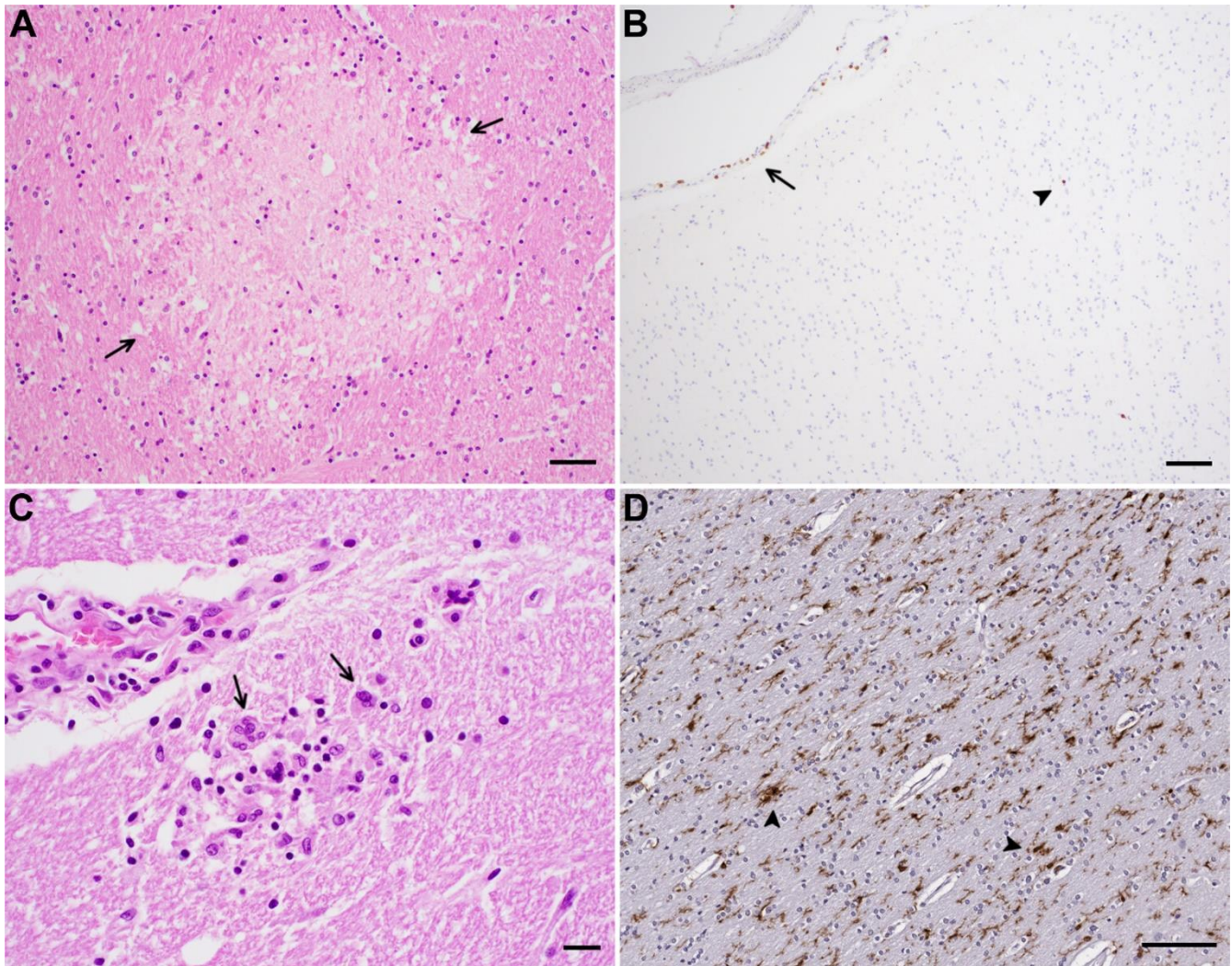


Figure 1. Neuropathologic findings in COVID-19 and HIV infection. **A)** Acute/subacute microinfarct (arrows) in the internal capsule and **B)** sparse leptomeningeal (arrow) and parenchymal (arrowhead) T lymphocytes highlighted by CD3 immunohistochemistry in patients with COVID-19. **C)** HIV encephalitis with multinucleated giant cells (arrows) and **D)** microglial activation (arrowheads) highlighted by immunohistochemistry for Iba-1 in patients with HIV infection. Scale bars: A = 50 μ m, B,D = 100 μ m, C = 20 μ m

with and without dementia as well as with and without HIVE [64,102]. Several gene expression profiling studies performed on the brains of HIV positive individuals have found upregulation of endothelial cell type transcripts [103] and dysregulation of microglial transcripts [104] in patients with HAND but without HIVE and increased expression of a subset of cytokines in white matter [103–107].

Although HIV antigen can be detected throughout the CNS including the cerebral hemispheres, cerebellum, brainstem, and spinal cord using various methods such as immunohistochemistry, in situ hybridization (ISH), PCR, and electron microscopy, the highest levels of HIV proteins, RNA and DNA,

primarily in macrophages, microglia and multinucleated giant cells, have been seen in deep gray matter and hippocampus [67,81,108,109]. Even with viral suppression on cART, low levels of HIV-1 RNA and anti-HIV antibodies can be detected in the CSF [110,111]. HIV-1 DNA, including intact proviruses, and RNA have been found in the brains of virally suppressed HIV-positive individuals in microglia/macrophages [112–114]. These reservoirs have been postulated to cause chronic inflammation and neuronal dysfunction [114,115], and microglial activation and increased cytokine levels in the brain have been shown to correlate with HAND [94,116–119]. However, although levels of HIV-1 DNA are on average higher in brains from patients

with AIDS compared to patients without AIDS, there is overlap [18,117]. Brain viral load correlates poorly with neuropathologic changes or cognitive impairment [94,117]. Furthermore, Gelman et al. have shown that subjects with HAND and HIVE have higher brain HIV RNA and DNA levels than patients without HAND, but individuals with HAND without HIVE show no difference compared to patients without HAND [88]. Thus, complex mechanisms beyond viral replication in the brain likely underlie HAND, especially in the post cART era (Figure 2) [56,84,120,121].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

A few weeks after a cluster of viral pneumonia cases, later called COVID-19, was first described in December of 2019 in China [122–124], the causative agent was determined to be a new human pathogen, the coronavirus later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [123]. Several vaccines were rapidly developed within a year and a significant proportion of the

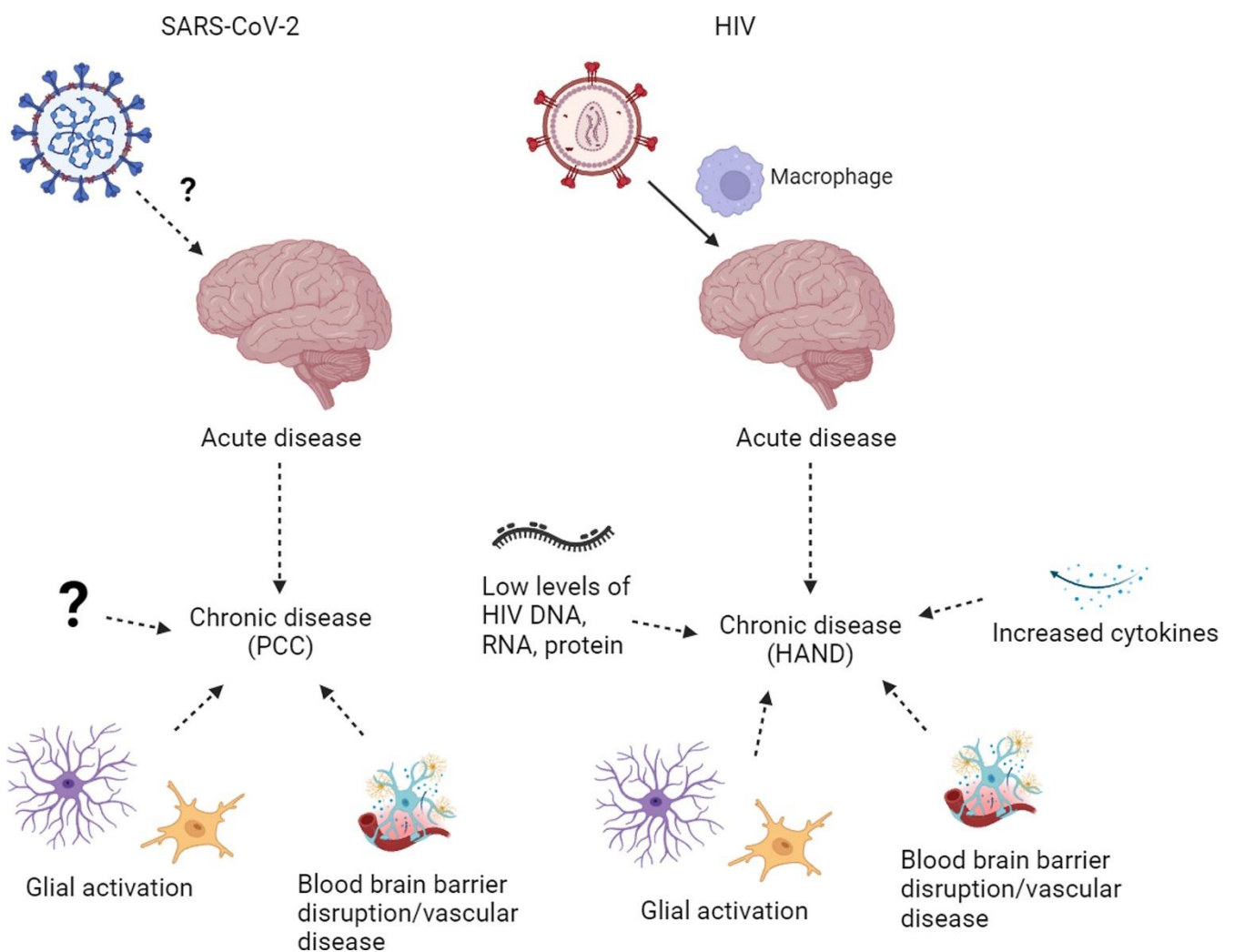


Figure 2. Potential mechanisms of neurologic disease in acute/chronic HIV infection and COVID-19/PCC. HAND, HIV-associated neurocognitive disorders; PCC, post-COVID conditions. Figure was created using BioRender.

population of many countries, mostly high-income, have been vaccinated, albeit with large differences among countries [122,125,126]. However, there have been approximately 6.9 million deaths and over 750 million infected worldwide according to the World Health Organization (WHO) [127].

Coronaviruses are classified into four distinct genera: Alpha, Beta, Gamma and Deltacoronavirus [128]. SARS-CoV-2 and SARS-CoV belong to the same species, severe acute respiratory syndrome-related coronavirus (SARSr-CoV), which is of the subgenus Sarbecovirus, genus Betacoronavirus which also includes Middle East respiratory syndrome coronavirus (MERS-CoV), of the subfamily Orthocoronaviridae [128,129]. During its spread several SARS-CoV-2 variants have emerged, termed “variants of concern”, including Alpha, Gamma, Delta, and Omicron, that have caused disease of similar severity except for Omicron which has been associated with lower rates of hospitalization [128,130].

SARS-CoV-2 predominantly infects nasal or upper respiratory epithelium and sustentacular cells of the olfactory mucosa [131–134] with a decreasing gradient of infection from the proximal to distal respiratory tract [135]. As with SARS-CoV, SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as the obligate receptor for host cell entry through binding of the viral spike (S) protein, proteolytically activated by transmembrane protease/serine subfamily member 2 (TMPRSS2), although ACE2-bound virus can also enter the cell via clathrin-mediated endocytosis without TMPRSS2 [129,136–140]. ACE2 is a human homologue of ACE, and both ACE and ACE2 play important roles in the renin-angiotensin system [141]. ACE2 mRNA has been reported in many different organs including, at least in some studies, the brain [142–145]. However, mRNA and protein levels of ACE2 have been shown to be discordant [146]. ACE2 protein has been detected in several cell types including ciliated cells of the nasal mucosa and bronchus, cardiomyocytes, enterocytes of the gastrointestinal tract, gallbladder epithelium, kidney proximal tubule epithelium, and Sertoli and Leydig cells of the testis [143,146,147]. In the brain, ACE2 protein expression has been seen by immunohistochemistry in vascular smooth muscle cells and/or endothelial cells/pericytes in some studies but not others [143,147–151]. Few studies have reported

ACE2 immunopositivity in choroid plexus, ependymal cells, meningotheial cells, and neurons in the medulla [151,152].

Neurologic manifestations

Approximately a third of patients with acute COVID-19 exhibit neurologic and psychiatric manifestations, most commonly fatigue, alterations in consciousness, impairment in smell and taste, seizures, myalgia, anxiety, and stroke [153–156]. Ischemic stroke is seen in approximately 2 % of COVID-19 patients [153–156], and occurs in younger individuals compared to ischemic stroke in non-COVID-19 patients [157]. Moreover, patients with COVID-19 have increased risk for ischemic and hemorrhagic stroke compared to patients with influenza or other upper respiratory tract infections [155,158], and increased risk for ischemic stroke and myocardial infarct compared to the background population in Sweden [159]. Neurologic manifestations have been associated with increased mortality, especially in older individuals [154,156].

Neurologic and psychiatric complications are also seen as part of the constellation of post-COVID conditions (PCC), also known as post-acute sequelae of COVID-19 (PASC) or long COVID, defined by the WHO as persistent symptoms usually 3 months from onset of COVID-19 with symptoms lasting at least 2 months with no alternative diagnosis [160–162]. Most frequent neurologic manifestations of PCC include fatigue and cognitive impairment, impaired concentration or “brain fog”, which has been shown to correlate with abnormal brain activation on task-activated blood oxygenation level-dependent functional MRI (BOLD-fMRI) [163], as well as psychiatric disorders such as post-traumatic stress disorder, anxiety and depression [164,165]. Similar complications were seen in the SARS 2003 pandemic [166], and post-viral syndromes occur in other viruses [167]. Cognitive decline and psychiatric symptoms have also been described after serious illness requiring admission to the intensive care unit such as sepsis [168,169]. However, examining the electronic health records of the US Department of Veterans Affairs, Al-Aly et al. found a higher burden of both pulmonary and extrapulmonary disease, including neuropsychiatric and cardiovascular disorders, in patients who had been hospitalized for COVID-19

and survived for at least 30 days after admission compared to individuals hospitalized for influenza [170]. A different study using electronic health records of health care organizations mostly in the US found that neurologic and psychiatric diagnoses are more common in the 6 months following the diagnosis of COVID-19 compared to other respiratory infections such as influenza [155]. PCC can occur regardless of the severity of acute disease but is more severe in hospitalized patients, and those with comorbidities appear to be at increased risk not only for acute disease but also for PCC [160,164,171]. Vaccination may be less effective at preventing PCC than severe acute COVID-19 [172]. Further clinical phenotyping of PCC, as with HAND in HIV, may be helpful in further defining research nosology [24].

Brain MRI findings in patients with acute COVID-19 presenting with neurologic symptoms include acute/subacute infarct, which is the most common finding, abnormalities of the olfactory bulb, white matter abnormalities, cerebral microbleeds, gray matter abnormalities, leptomeningeal enhancement, acute disseminated encephalomyelitis (ADEM) and ADEM-like lesions, intracerebral hemorrhage, and posterior reversible encephalopathy syndrome (PRES) [173,174]. In ¹⁸F-FDG PET studies, subacute COVID-19 patients have shown hypometabolism in the frontoparietal cortex, which correlated with cognitive performance, with reduction in hypometabolism along with improvement in cognitive performance approximately 6 months after onset of symptoms [175,176]. In a large longitudinal study examining participants in the UK Biobank who had undergone repeat imaging, a decrease in gray matter thickness in the orbitofrontal cortex and parahippocampal gyrus as well as decrease in global brain size were seen between two scans in those who had been infected by SARS-CoV-2, likely with different variants and averaging 4-5 months after infection, compared to those who had not been infected by SARS-CoV-2 [177]. Greater cognitive decline was also seen in the SARS-CoV-2 positive group [177]. Subsequently, Du *et al.* found that male patients demonstrated reduced gray matter thickness in the parietal and occipital cortices and hippocampal volume after Omicron infection compared to before infection [178]. In patients

diagnosed with PCC, gray matter volume loss has been associated with cognitive dysfunction [179].

Neuropathologic findings

Brain autopsy examination of patients who died from COVID-19 have shown a variety of neuropathologic findings, although many are non-specific [180–184]. Most commonly seen are acute hypoxic-ischemic changes with neuronal eosinophilia, acute/subacute infarcts (Figure 1) with macrophage infiltration and neovascularization, hemorrhage [149,185–191], microthrombi [192–194], astrogliosis and microglial activation occasionally with microglial nodules and neuronophagia especially in the cerebellum and brainstem [185,195–199], and T-lymphocytic infiltration, predominantly sparse in a perivascular distribution [180,182,185,186,193,195,200,201]. Similar features including hypoxic-ischemic injury, microinfarcts, hemorrhage, and sparse lymphocytic infiltrate as well as fibrinogen leakage were seen between Delta, Omicron and non-Delta/non-Omicron variants [202].

Other findings described in patients who died from acute COVID-19 infection include perivascular hemosiderin deposition/leakage [182,193], though perivascular hemosiderin deposition is a common finding in autopsy brains, especially in older individuals, and can be seen in both brains with and without significant vascular disease [182,203–206]. They have also been shown to correspond to a subset of cerebral microbleeds on MRI [207]. Megakaryocytes in cortical capillaries and in an infarct were also reported in acute COVID-19, but capillary megakaryocytes can be seen in the setting of lung injury due to a variety of causes [208–210]. Uncommon findings include multifocal necrotizing leukoencephalopathy [185], acute encephalitis with lymphohistiocytic infiltrate and hemorrhage [200], and ADEM/acute hemorrhagic leukoencephalopathy (AHLE) and ADEM/AHLE-like pathology [149,195,211–213]. Some comorbid neuropathologic findings described include other infections such as HSV-1 encephalitis [185] and bacterial infection [193], neurodegenerative diseases including Alzheimer disease and Lewy body disease [185,195], and cerebrovascular disease such as cerebral

amyloid angiopathy [210], not surprising given the older patient age in some series [185,195,200,214].

Few studies have compared brains from COVID-19 patients to controls [152,197,198,200]. No differences in frequencies of hypoxic-ischemic changes, infarcts or hemorrhages were seen between COVID-19 and non-COVID-19 patients in one study [200]. In another study, perivascular and leptomeningeal T-lymphocytic infiltrates were seen in both COVID-19 patients and in controls with sepsis /systemic inflammation, and microglial, activation in the pons in COVID-19 patients was greater as compared to controls without sepsis but similar to controls with sepsis [152]. However, Lee *et al.* showed that the brains of COVID-19 patients demonstrate increased leakage of fibrinogen, consistent with BBB disruption, complement activation and microthrombi compared to controls, supportive of neurovascular injury [198,215]. Leakage of fibrinogen and other serum proteins in the brain in COVID-19 have also been reported [150,202]. Several gene expression profiling studies on various regions of the brain from COVID-19 patients have shown downregulation of neuronal and synaptic pathways in the olfactory bulb and amygdala [200], dysregulation that overlap with aging and neurodegenerative diseases in the frontal cortex [145,216], metabolic dysregulation in the brainstem [198], and inflammation in the choroid plexus [145,217]. Very few autopsy studies have examined patients who recovered from COVID-19 prior to death; these have also shown microglial activation/macrophages [195,197]. One of the studies included two patients with mild COVID-19 symptoms who died 4-5 and 10 weeks after testing positive for COVID-19 from causes unrelated to the infection [197]. In these subjects microglial activation/macrophages were also seen, similar to findings in patients with acute COVID-19 in the brainstem and cerebellum but to a milder degree in the cerebral white matter [197]. So far there have been no autopsy studies of patients diagnosed with PCC (long COVID).

In a brief look at other pandemics, hypoxic-ischemic changes, infarcts, hemorrhage, microglial activation, and ADEM-like lesions were also seen in autopsies of patients who died from the novel influenza A H1N1 virus in 2009 [218]. The few autopsies reported on SARS-CoV, the etiologic agent responsi-

ble for the SARS pandemic which emerged in 2002 [219], described hypoxic-ischemic changes and gliosis in the brain [220,221]. There are only rare reports of SARS-CoV detected in the CSF [222,223] and in brain using PCR, ISH, immunohistochemistry, and electron microscopy [220–222,224] with isolation of SARS-CoV reported from the brain of one patient [221]. The “brain isolation” may have reflected isolation of virus from brain vasculature.

Although several studies have detected SARS-CoV-2 RNA in the brain using PCR or transcriptomic analysis [152,185,193,200,225–227], including in the affected area of a case of hemorrhagic encephalitis possibly attributed to COVID-19 [200], other studies have not detected viral RNA or protein in the brains of patients with COVID-19 using a variety of methods [145,182,186,192,195,197,198,201,216,217], and SARS-CoV-2 has never been cultured from brain [131,180]. Few studies have performed cellular localization of viral RNA using ISH or viral protein using immunohistochemistry and most have shown that they are restricted to vessels/near vessels such as in endothelium, within macrophages or near capillaries [148,182,225,228]. There are rare reports of viral protein or RNA in brain tissue or cranial nerves [148,182,185,229–231], including a report by Thakur *et al.* which found low levels of viral RNA by RT-PCR but no viral RNA or protein by RNAscope and immunohistochemistry [185]. Viral RNA was seen in the adventitia of a meningeal blood vessel outside the medulla in one case [185]. Because of frequent anosmia/hyposmia and olfactory dysfunction in COVID-19, the suspicion is that the virus may enter the brain via the olfactory route through the cribriform plate, similar to neurotropic viruses [232–234]. Several studies have examined the olfactory bulbs [185,193,201,230,231,235]. Most showed variable degrees of T-lymphocytic infiltration and gliosis without presence of viral protein, but variability in presence of viral RNA in human tissue [185,193,201,230,231,235].

These discrepancies may partly be due to differences in patient cohorts and methods employed including the usage of different commercial antibodies. Some antibodies, including a widely used spike antibody (Abcam 3A2), have subsequently been shown to label vessels and neurons in both COVID-19 and control patients or have high background

[145,180,197,236]. Viral nucleocapsid antigen and RNA have only rarely been detected in CSF in acute disease [237–240]. CSF analysis often shows slightly increased white blood cell counts as well as elevated albumin and protein levels and an elevated albumin quotient, which suggests disruption of the BBB [238]. Similar to the brain, SARS-CoV-2 has never been cultured from CSF even when virus could be grown from paired nasopharyngeal swabs [131]. In electron microscopy studies, virions have mainly been identified in the respiratory tract, and reports of ultrastructural detection of virus outside the respiratory tract are controversial due to potential misinterpretation of virus-like particles [236,241–243]. Thus, it is unclear whether SARS-CoV-2 is neurotropic or neuroinvasive, and mechanisms other than direct infection likely contribute to both acute and chronic forms of the disease (Figure 2) [167,232].

Conclusions and next steps

HIV and SARS-CoV-2 are associated with significant neurologic morbidity but with differing pathogenesis underlying acute and chronic disease. In acute disease, HIV directly invades the CNS while SARS-CoV-2 may exert its effects more indirectly through systemic inflammation. In chronic disease, HIV persists in the brain despite cART, and sequelae of low-level infection may contribute to HAND [115]. PCC may also be associated with sequelae of inflammation, but in both diseases, complex interactions with comorbidities likely underlie neurologic manifestations [48,160]. Furthermore, both PCC and HAND have significant components of psychiatric disease in which functional abnormalities are thought to predominate over structural abnormalities [244,245].

Mechanisms of aging related neurodegeneration have also been implicated. Brain lysates from COVID-19 patients have shown activation of TGF- β signaling and increased oxidative stress as well as activation of pathways leading to tau hyperphosphorylation associated with Alzheimer disease [246]. One promising avenue of investigation is the cerebral vasculature, as vascular disease and BBB dysfunction have been implicated to play a significant role in HAND and acute COVID-19 [54,64,102,198].

Furthermore, it is well established that vascular disease plays a significant role in aging and neurodegenerative diseases [247], pathways which have been implicated in COVID-19 as well as HAND [145,216,248,249].

The following are potential “next steps” to elucidate the mechanisms underlying the neurologic manifestations in HAND and COVID-19/PCC discussed at the two meetings:

- Longitudinal studies of patients with HAND and PCC incorporating clinical, microbiology and pathologic findings using a multidisciplinary approach are warranted [250].
- Consensus on more sensitive and specific cognitive assessment tools for PCC will help in characterizing the clinical spectrum of PCC and guiding further investigation [251,252].
- Neuropathologic studies of patients with PCC in comparison to control groups using standardized guidelines and quantitative morphometric approaches, as has been done for HIV, may be helpful [251,253,254].
- As routine light microscopy may not be sensitive enough to detect subtle changes, more in depth molecular investigation in conjunction with histopathologic examination, as has been pioneered by several groups showing transcriptomic changes in both HIV and COVID-19, holds promise in shedding light on their neuropathogenesis [56,103,145].
- Greater funding is needed to perform labor and resource intensive rapid autopsies on patients with HAND and PCC as mRNA involved in the immune response are more susceptible to degradation from prolonged postmortem intervals [255,256].
- Additionally, increased use of formalin fixed paraffin embedded tissue for gene expression studies made possible by recent advances in technology will markedly expand human tissue available for research [198].

- Further consensus on more granular and precise neuropathologic assessment of vascular disease, which is of increasing interest to the neurodegenerative and neuropathologic community, is needed to assess vascular dysfunction in HIV and COVID-19/PCC [257].

A better understanding of the neuropathogenesis of neurologic complications in HIV and SARS-CoV-2 infection will help in the management of these patients.

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