# Central nervous system outcomes of COVID-19

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**The worldwide pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected an estimated 200 million people with over 4 million deaths. Although COVID-19, the disease caused by the SARS-CoV-2 virus, is primarily a respiratory disease, an increasing number of neurologic symptoms have been reported. Some of these symptoms, such as loss of smell or taste, are mild and non-life threatening, while others, such as stroke or seizure, are more critical. Many of these symptoms remain long after the acute illness has passed, a phenomenon known as "long COVID" or postacute sequelae of SARS-CoV-2 infection (PASC). Neurological symptoms can be difficult to study due to the complexity of the central and peripheral nervous system. These neurologic symptoms can be difficult to identify and quantitate. This narrative review will describe approaches for assessing neurologic manifestations of COVID-19, with examples of the data they provide, as well as some directions for future research to aid in understanding the pathophysiology of COVID-19-related neurological implications. (Translational Research 2021; 000:1–11)**

**Abbreviations:** ACE2 = angiotensin converting enzyme 2; ARDS = acute respiratory distress syndrome; CFS = cerebral spinal fluid; CNS = central nervous system; GBS = Guillain-Barre Syndrome; GFAP = Glial Fibrillary Acidic Protein; NfL = neurofilament light chain; ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome; PASC = postacute sequelae of COVID-19; PCR = polymerase chain reaction; PNS = peripheral nervous system; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UCH-L1 = ubiquitin carboxyl-terminal esterase L1; YKL-40 = Chitinase 3-like 1.

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus first described in Wuhan, China in December of 2019.[1] It is a member of the Coronaviridae family of viruses and causes the disease now known as COVID-19.[1] While the virus is primarily a respiratory virus, increasing evidence of neurologic involvement has emerged.[2] Neurologic symptoms range from mild, such as headache,[3-5] nausea,[6] anosmia,[7,8] ageusia,[7] altered consciousness,[9-11] "brain fog", to more severe such as myalgia, hemorrhage,[12] syncope,[9-11] seizure,[9-11] stroke,[13] meningoencephalitis,[14] Guillain-Barre syndrome (GBS)[15] and demyelinating disease.[14,16,17] The exact pathologic basis for these neurologic symptoms is not currently known, despite an abundance of published investigations.[18-26] Several possible mechanisms for neurologic involvement have arisen in the literature.[19,27,28] These include a direct viral invasion, a "Trojan horse" mechanism where the virus accesses the brain through circulating lymphocytes, a systemic inflammatory response and a coagulopathy-induced prothrombotic state.[19,27,28]

As summarized in Table 1, different approaches can yield insights into the pathobiology of neurologic complications of COVID-19. This article will present the strengths and limitations from different types of studies

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**Table 1.** Types of studies for neurological manifestations of COVID-19

| Type of study | Strengths | Limitations |
|---|---|---|
| Case report | Short rapid publications of single or small groups with novel medical findings. When enough groups are found, can yield insights into comorbidities and treatment plans. | Single patient or small number of patients may not be generalizable to larger groups |
| Observational studies | Generally, utilizes moderate to large-sized existing data sets, quite often from medical records, to look for trends and associations that are not obvious in smaller studies | Can be timely to obtain<br>Often requires expert review |
| Autopsy | Allows one to see inside of organs/brain<br>Can assess cause of death<br>Multitude of tissues available for structural, histological and immunological analysis. | A snapshot of end-stage disease<br>Does not inform on susceptibility or disease progression |
| Imaging studies | Allows examination of neural tissues in a live subject. | Expensive, non-routine<br>A snapshot in time unless repeated measures are made |
| Blood biomarkers | Easy to obtain specimens.<br>Circulates throughout the body and therefore has contact with a variety of organs tissues | May not reflect what is happening in specific tissues |
| Cerebral spinal fluid | Gives insights into central nervous system infection, blood brain barrier disruption | Can be difficult to obtain<br>Not routinely performed unless indicated |
| Self-report | Inexpensive<br>Easy to obtain<br>Gives information on symptoms, quality of life, mental status | More difficult to quantitate<br>Can be inaccurate |
| Animal models | Can gain more information on cause and effect.<br>Can see effects more quickly.<br>Can analyze tissue at different time points in the course of a disease.<br>Can add and remove proteins to see their effect. Can be used to test treatments. | Humans are not mice/primates, so data may not be generalizable. |
| In vitro modeling | Gives detailed mechanisms, which greatly informs treatment options. Tests treatment options. | Cannot take into account whole body affects. |

along with some major findings. Potential areas for future research are also discussed.

## CASE REPORTS

During the initial phases of the COVID-19 pandemic, one of the main sources of information for physicians and scientists came from case reports. These brief reports gave much needed insight into the progression of the disease in hospitalized patients and a glimpse into potential treatment regimens. These early reports provided the first indications of neurologic symptoms in this respiratory disease.

For example, Wada et al[29] reported the case of a 69-year-old male patient who presented with pneumonia from SARS-CoV-2 infection and was intubated on Day 3 after admission. On day 17, despite improvements in respiratory condition and removal of anesthetic drugs, no cough reflex was noted, and tendon reflex was diminished. Based on these symptoms, the authors suspected GBS and treated with intravenous immunoglobulin (IVIG). On day 23, the cough reflex improved, and the patient was extubated. This case report briefly described symptoms to watch for and efficacy of the treatment regimen utilized in this case. In a meta-analysis of GBS associated with COVID-19, Palaiodimou et al[30] examined 18 studies with a total of 136,746 COVID-19 patients and found a prevalence rate for GBS to be approximately 15 cases per 100,000 SARS-CoV-2 infections and demonstrate that COVID-19 associates with an increased likelihood of GBS and with demyelinating Guillain-Barre variants.

An early case report describes a 78 year old male patient whose main complaint at admission was acute confusion, behavioral disorders, and cognitive troubles.[31] The physical exam, blood and cerebral spinal fluid (CSF) tests were unremarkable. An EEG showed

an evocative pattern of encephalitis. The patient later tested positive for SARS-CoV-2. This case report indicates that not all cases of COVID-19 present with respiratory symptoms.

Case reports by Faber et al,[32] Cohen et al,[33] and Mendez-Guerrero et al[34] reported a COVID-19 associated Parkinsonism. While parkinsonism has been reported following other infectious diseases, these COVID-associated cases are suggestive of an infection-related cause of the parkinsonism. Brundin et al[35] highlight potential mechanisms for the rapid development of parkinsonism following COVID-19 infection, and the potential for a pre-disposition to parkinsonism in SAR-CoV-2 positive people later in life.

In a systemic review and meta-analysis of people with COVID-19, de novo seizures and epilepsy, Asadi-Pooya et al[36] noted that persons with epilepsy and other pre-existing neurological disorders who contracted COVID-19 were more likely to develop exacerbation of their neurological problem and to have more severe infections. They also noted the presence of new onset seizures in people with COVID-19 that can potentially extend beyond the acute phase of the infection.

As the pandemic progressed, review articles have been useful in combining available case reports and case studies.[24,25,36-45] These reviews were key to demonstrating prevalence of neurologic manifestations[46] among COVID-19 patients and to assess the prevalence of SARS CoV-2 presence in CSF as assessed by polymerase chain reaction (PCR) or serologic testing.[47] A precautionary note in examining these data is the inability to assess the comparability of PCR or serologic testing across facilities in order to harmonize the data. The viral RNA levels determined by PCR in the CSF, where positive, are generally very low compared to amounts found at other sites (ie, nasopharynx) and differences in the testing protocol and reagents utilized may explain differences in results reported.

While these case studies and reports are important in describing early neurological manifestations of COVID-19 and some insight into potential therapies, they are individual or small group cases with individual comorbidities that may or may not be generalizable to the greater population and generally only describe patients with moderate to severe symptoms.

**Observation studies.** One of the first retrospective observational case series by Mao et al[48] used clinical data extracted from electronic medical records at 3 specialized COVID-19 care centers in Wuhan, China. The study contained 214 lab confirmed cases of COVID-19, 88 of whom had severe infection according to their respiratory status. Of these 214 patients, 78 (36.4%) had neurologic manifestations, with more symptoms present in the severe cases. Neurologic symptoms reported were dizziness, headache, impaired taste, smell, vision, and level of consciousness. Acute cerebrovascular disease, with central and peripheral nervous system involvement were also observed. Apart from cerebrovascular disease (1-18 days) and loss of consciousness (1-25 days), symptoms appeared within the first 1-2 days after admission. Patients with more severe illness had a higher incidence of acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury than those with less severe illness.

Observational studies from various countries showing neurological manifestations of COVID-19 have since been reported. Rifino et al[49] reported that in Bergamo, Italy, major neurological manifestations were observed in 137 patients out of the 1760 hospitalized between February 23, 2020 and April 30, 2020, 39 of which presented with neurological symptoms. They reported 53 cerebrovascular manifestations, 31 peripheral nervous system manifestations and 49 patients with altered mental status. Included are "Clinical Vignettes" sections that resemble case reports on specific patients. Garcia-Azorin et al[50] reported neurological manifestations from the Spanish Society of Neurology Registry on 233 patients reported between March 2020 and July 2020. The major complaints were stroke (n=63), altered mental status (n=55), neuromuscular symptoms (n=55) and anosmia (n-41). They also report that anosmia and headache generally occur early in the disease progression (average 2-4 days) while neuromuscular symptoms and stroke occur later (average 11-14 days).

Flores-Silva et al[51] examined 1072 consecutive COVID-19 positive cases from March 15, 2020 through June 30, 2020 in Mexico City and found 71 patients with pre-existing neurologic diseases (mostly diabetic nephropathies and epilepsy), and 163 patients who developed new neurologic manifestations from COVID-19 exposure. At presentation, major complaints were headache (42%), myalgia (40%), dysgeusia (8%) and anosmia (7%), while hospital-developed complaints were delirium (13%), limb weakness (5%) and delayed mental status recovery (2.5%). Patients with neurologic complaints, compared to those hospitalized without neurologic complaints, were more likely to have dyspnea, elevated hemoglobin, white cell count, neutrophil count, creatinine levels, BUN, LDH, CRP, fibrinogen and d-dimer, and lower lymphocyte count and albumin levels.

Frontera et al[52] examined 4491 patients in New York City from 3/10/2020 to 5/10/2020 and found that 13.5% developed new neurologic disorders. Most common were encephalopathies (51%), seizure (12%),

stroke (14%) and hypoxic/ischemic injury (11%). Of the 18 CSF samples analyzed none were positive for the virus by PCR testing.

In another observational study, Bain et al[53] compared patients with COVID-19 related acute respiratory distress syndrome (ARDS) to pre-COVID-19 patients with viral ARDS, bacterial ARDS or culture negative ARDS. The COVID-19 patients were more likely to be black, reside in nursing facilities, have higher BMI, have lower initial IL6 levels and be on mechanical ventilation longer than patients experiencing other types of ARDS. The 60-day mortality rates were similar between all groups regardless of the cause of ARDS. This study highlights another hurdle in studying COVID-19: what to use as a control group. With the government lockdowns that occurred at the onset of the pandemic, being COVID-19 negative may just indicate that you were not exposed. And in early stages of the disease, only symptomatic people were tested for the virus, so many asymptomatic positive people were never tested. Utilizing serologic assays for the presence of antibodies would yield information about asymptomatic, exposed individuals, but care must be taken with the onset of vaccination to distinguish between vaccine-acquired antibodies and infection acquired antibodies.

**Autopsy.** Autopsy studies have proven useful, particularly in early stages of COVID-19. Several common brain findings on autopsy from COVID-19 deaths were edema, meningeal congestion, acute hypoxic ischemic damage and multiple large and small infarcts.[9,54,55] The presence of virus in the brain yielded mixed results, with Meinhardt et al[56] finding the highest levels in mucosa sampled from directly under the cribriform plate, while Matschke et al[57] found SARS-CoV-2 RNA in 53% of autopsied brains. Discrepancies can be due to differences in time to autopsy, presence of fixatives, markers assessed and methodologies. Interpretation of these data must proceed with caution, as the number of autopsies that include brain data are extremely limited, in part because COVID-19 primarily manifests as a respiratory illness, so the brain was not analyzed and/or because of COVID-19 safety restrictions limiting the harvesting and storing of potentially infectious brain material.

**Imaging.** Neuro-imagining studies are key to understanding pathophysiology of COVID-19 prior to death. That approximately one third of COVID-19 patients report neurologic complications, brain imaging is key to exploring potential complications. Chowdhary et al[58] performed a systematic review of imaging studies and reported that of the 171 patients with neuroimaging data, 36% had ischemic stroke, 26% had CNS inflammatory disorder, 24% hemorrhagic stroke, 14% encephalitis, 6% with encephalopathy and 3.2% with GBS. While only 3 patients showed signs of olfactory bulb enhancement, their age was significantly younger (mean 29, SD 5.3) than those without (mean 53.6, SD 15.4). Imaging also revealed significantly higher fatality in those with a vascular neuropathology than in those without.

Egbert et al[59] reviewed early neuroimaging studies that included CT, EEG, MRI and PET scans. Out of 361 reviewed cases, 124 showed brain abnormalities. The most frequent abnormalities noted were white matter hyperintensity on MRI (53%) and hypodensities (24% on CT scan). These white matter abnormalities were most often found in the bilateral anterior and posterior cerebral white matter. Additionally, micro-hemorrhage, hemorrhage and infarcts were also evident.

While these neuroimaging studies shed light on brain anomalies that may explain COVID-19 neurologic symptoms, a lack of pre-pandemic imaging prevents understanding whether SARS-CoV-2 caused the anomalies, or the anomalies were exacerbated by SARS-CoV-2.

**Blood biomarkers.** The availability of blood-based biomarkers that can assess traumatic brain injury, blood brain barrier integrity and axonal injury or degradation without the need for CSF has been a major focus of many researchers, especially in Alzheimer's Disease and related dementia.[60] Recent advancements include total Tau, phosphorylated tau-181 (pTau-181), pTau-217, neurofilament light (NfL), Glial Fibrillary Acidic Protein (GFAP), ubiquitin carboxyl-terminal esterase L1 (UCH-L1), and Chitinase 3-like 1 (YKL-40). In an observation study, Kanberg et al[61] measured GFAP and NfL in COVID-19 patients with varying severity of illness and age/sex matched controls. They found elevated GFAP in moderate and severe COVID-19 cases compared to controls and elevated NfL in severe cases. Patients with mild disease had levels comparable to controls. Both markers are known to increase with age. In COVID-19 patients, NfL was negatively correlated with lymphocyte count and neither marker correlated with C-reactive protein (CRP). DeLorenzo et al[62] studied 104 COVID-19 positive blood samples collected at hospital admission. They found higher levels of NfL, GFAP and total Tau in those patients that died and higher NfL and UCH-L1 in those that required ICU admission. In a survival analysis, they found that those patients with total Tau levels above the median were more likely to die (50% probability) than the patients with Tau levels below the median (10% probability) at 40 days. There are many studies of COVID-19 biomarkers in the blood, such as cytokines and chemokines, but few compared blood biomarkers with neurologic manifestations. Sun et al[63] did look at blood

biomarkers with neurologic manifestations and saw little difference between groups. Mazza et al[64] demonstrated an association of the systemic immune-inflammation index (SII = (neutrophils x platelets)/lymphocytes) with self-reported depressive symptoms and poorer cognitive scores at 3-months post hospital discharge. In general, these studies are small and show post-infection data, but without historic data they cannot determine cause (susceptibility) vs effect.

**Cerebral spinal fluid.** A review by Lewis et al[47] identified 430 patients with COVID-19 diagnosis based on PCR or serologic testing who had neurological symptoms prompting CSF testing. Seventy-five percent had symptoms that localized to the CNS and 25% had symptoms that localized to the peripheral nervous system (PNS). The most common symptoms that precipitated CSF testing was encephalopathy/coma (56%). Of the 409 patients who had CSF white blood cell counts evaluated, 66% had detectable WBC or were noted to have pleocytosis, which may be indicative of infection, inflammation, or other CNS injury. Protein levels in the CSF were reported for 397 patients, 40% of whom had protein >60 mg/dL or were noted to have increased protein concentration. This can be indicative of axonal injury, the presence of inflammation or the existence of intrathecal antibodies. Sars-CoV-2 PCR testing was performed on CSF from 303 patients, with 6% testing positive, all of whom had CNS-localized symptoms. CSF antibody testing was performed on 58 patients and 72% tested positive for antibodies to SARS-CoV-2. Thirty-two of these patients had further testing to determine if the antibodies were produced intrathecally or transmitted to the CSF due to blood brain barrier disruption. Of these patients, 22% had results consistent with intrathecal antibody synthesis, while the remaining 78% did not. Autoimmune antibodies were found in the CSF of 5% of the 77 patients tested. Increased CSF IL6 levels were reported in 20/27 patients tested and 16/17 patients tested had elevated CSF IL8. The different results seen across studies could be indicative of differences in testing protocols used, differences in neurological symptoms that prompted the collection of CSF, variability of CSF protein and antibody levels based on length of symptoms, traumatic lumbar puncture or truly an indication of SARS-CoV-2 virus in the CSF. The data imply that for the majority of patients with neurological symptoms and CSF data, the SARS-CoV-2 virus does not directly infect the CNS.

**Self-report.** Much of our current data relies on patient self-report of symptoms and previous medical history. Neurological manifestations, such as headache, fatigue, "brain fog", can be difficult to quantify. Analogies to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) which manifest in years of patients reporting a multitude of debilitating symptoms that cannot be easily quantitated or validated to their primary physicians is noted.[65]

In a study by Soraas et al,[66] 794 SARS-CoV-2 positive, 7978 SARS-CoV-2 negative and 4229 randomly selected untested participants, none of whom were hospitalized, were given a questionnaire for self-reporting symptoms within a few weeks of initial SARS-CoV-2 testing (February − April 2020) and another questionnaire 8 months later. The baseline questionnaire showed higher reports of fever, dyspnea, cough, fatigue, anosmia or ageusia in the SARS-CoV-2 positive participants than the negative participants, while the randomly selected untested participants were lower still. On 8-month follow-up, 11% of SARS-CoV-2 positive participants reported memory problems in the past 3 weeks, compared to 4% in the SARS-CoV-2 negative group and 2% in the random sample. The health-related quality of life indicators at 8-months showed similar responses between the positive and negative groups, with the exception of question "worsening self-reported health in the past year" which was 41% for positive group, 21% for the negative group and 12% for the random sample. Both of the tested groups were higher than the random group for all quality of life questions.

Havervall et al[67] examined healthcare workers in Stockholm Sweden who were enrolled between April 15 and May 8, 2020 to do an 8-month follow-up questionnaire on long-term symptoms, with 323 who tested positive for SarS-CoV-2 and 1072 who tested negative. Their primary goal was to examine the extent and duration of long-term symptoms. In the Sars-CoV-2 positive group, 14.9% had symptoms remaining at 8 months, compared to the negative groups (3.4%), with the most common moderate to severe symptoms in the positive group being anosmia, fatigue, ageusia and dyspnea.

Davis et al[68] used an on-line survey of participants (n=3762), mostly from COVID support groups to examine long-term symptoms and quality of life indicators. This group had 1020 confirmed cases and 2742 suspected cases prior to June 2020 and reported that after 35 weeks, they still had an average of 55.9 symptoms over 9.1 organs. A reduced work schedule was requested by 45% and 22% report they were not working due to their illness, showing the debilitating effects of Sars-CoV-2 virus.

Elkan et al[69] performed a post-COVID online survey for sequelae using the RAND-36 health survey examining 66 COVID-19 patients hospitalized with pneumonia to 42 age and sex matched COVID-19 negative patients hospitalized with pneumonia. The negative group were more likely to be smokers and have chronic

lung disease while the positive group had a longer hospitalization. At 9-month follow-up, the positive group had low scores, indicating worse symptoms, for pain, general health, vitality and health change, with the largest difference between the groups being in the health change score (positive=25 and negative=50).

Wanga et al[70] examined an internet survey of 3135 people (698 positive, 2437 negative) who had COVID testing performed through April 2020. The positive group were younger, employed, more urban and had higher income than the negative group. The positive group reported having long-term symptoms (65.9%) while the negative group reported 42.9%. The major symptoms were fatigue, change in smell/taste, dyspnea and cough. Post-vaccination data (n=100 positive, 285 negative) on long-term symptoms indicated that 28.7% of the positive group thought the vaccine made their symptoms better vs 15.7% in the negative group. However, 16% of the positives and 11 % of the negatives report that the vaccine made the symptoms worse.

This self-report data indicates just how difficult it is to study long-term effects of COVID, particularly in the neurological realm, as a true control is difficult to find when the pandemic affected everyone regardless of their sero-status. Lockdowns, fear and isolation effects in negative cases are evident in these surveys.

**Animal models.** With the onset of the COVID-19 pandemic, the push was on for appropriate animal models to better understand disease pathogenesis, aid in vaccine development and test therapeutics. Previous mouse and rat models developed for SARS-CoV proved ineffective for the current pandemic as the SARS-CoV-2 does not bind to mouse and rat ACE2 receptor. This led to the need to induce COVID-19 through genetic adaptation of the SARS-CoV-2 virus by the production of chimera between the SARS-CoV and SAR-CoV-2 viruses, the use of ACE2 knock-ins and transgenic mice, and viral-transfection of wild-type mice with human ACE2.[71,72] Using a K18-hACE2 transgenic mouse model, Zheng et al[73] were able to infect mice showing symptoms in lungs and occasionally brains. They saw evidence of vasculitis and thrombosis in mice with severe pneumonia. Pre-treatment with convalescent plasma protected against lethal disease but did not prevent anosmia.

**In vitro modeling.** One of the controversial questions is whether SARS-CoV-2 can directly infect endothelial cells.[74] Early studies using immuno-histologic staining or electron microscopy seemed to show the presence of infected endothelial cells and the presence of detectable viral RNA or spike proteins in the endothelium seemed to support this notion. In contrast, basic science methods such as in-situ detection, cell culture-based assays, and tissue-specific sequence analysis generally indicate that few, if any, endothelial cells are infected.[75-80] He et al[81] have found that pericytes express ACE2 to a greater extent than endothelial cells and hypothesize that previously compromised endothelium, as found in hypertension, diabetes and obesity (main comorbidities for COVID-19), increases pericyte exposure and promotes virus-pericyte interaction.

Single-nucleus transcriptomes (65,309) were profiled using snRNA-seq techniques from frontal cortex and choroid plexus samples from 8 COVID-19 positive and 14 control patient post-mortem tissues.[82] No molecular evidence of SARS-CoV-2 was observed in the brain. Broad cellular perturbations indicated that barrier cells of the choroid plexus may sense and relay peripheral inflammation into the brain and that peripheral T cells can infiltrate the parenchyma. Additionally, subpopulations of microglia and astrocytes observed in the COVID-19 samples share features with other previously characterized neurodegenerative diseases.

Schwabenland et al[83] used highly multiplexes high-dimensional imaging mass cytometry (IMC) in post-mortem COVID-19 positive samples. They identified the accumulation of distinct microglial and T cell subsets in microglial nodules and the perivasculature using deep spatial analysis of postmortem brain tissue, specifically examining the brain stem and olfactory bulbs. Neural inflammation was observed with axonal damage, compromised blood-brain barrier, and virus-associated perivascular inflammation. Their data showed profound immune activation with specific CD8 T cell clusters affecting the vasculature, and CD8 T cell-microglial crosstalk in the parenchyma. They also report SARS-CoV-2 specific viral antigen in the ACE2-receptor positive cells that were enriched in the vascular compartment.

Using 3-D tissue-engineered microfluidic in-vitro model of the human blood-brain barrier, Buzhdygan et al[84] found that the SARS-CoV-2 spike protein (S1) increases the blood brain barrier permeability. They also utilized cultured human brain microvasculature endothelial cells to show that the S1 protein upregulates cell adhesion molecules (ICAM-1, VCAM-1), inflammatory chemokines (CCL5, CXCL10), and matrix metalloproteinases (MMP3, MMP12).

**Long-term outcomes.** Pezzini et al[85] examined hospitalized ischemic stroke patients in Lombardy Italy from March 2020 through April 2020, comparing those who were COVID positive to those who were negative. The stroke patients who were positive for COVID were more likely to have cardiac embolism, atrial fibrillation, have lower rates of smoking and hypertension and were more likely to die.

Blomberg et al[86] followed COVID-19 positive patients and seronegative, exposed controls in Bergin,

Norway for 6 months, with 247 who isolated at home and 65 who were hospitalized. Over 50% of the participants still had symptoms at 6 months. Those under 30 years of age were most likely to complain of disturbed taste or smell and fatigue, while those over 30 also had concentration and memory problems with increased frequency with increasing age.

Frontera et al[87] followed 606 COVID positive patients with neurological symptoms compared to 3885 COVID positive patients without neurological symptoms in the New York City area. Among those with neurological symptoms, 211 died and 196 completed their 6 months' follow-up, compared to 75 deaths in the non-neurological group. An age and sex matched control group with 6 months' follow-up was established. Those patients with neurological symptoms were more likely to have a history of neurological findings, were more likely to develop acute renal failure, were more likely to be discharged to a nursing facility rather than home, had longer hospital stays and were less likely to return to work. Neurological complications were an independent predictor of limited activities in daily life.

Graham et al[88] studied 100 patients at a Chicago, Illinois neurology clinic, 50 who had tested positive for COVID and 50 who tested negative. Major comorbidities were depression/anxiety (42%) and autoimmune disease (16%). As with other reports, the major neurological manifestations reported in the positive group were brain fog (81%), headache (68%), numbness/tingling (60%), dysgeusia/anosmia (55%) and myalgia (55%). They assessed several quality of life indicators, and saw no significant difference between the positive and negative groups, but both groups were significantly lower than the normative median score for cognition and higher than the median score for fatigue. The COVID positive group alone scored lower than the normative median for attention and working memory. This data indicates the difficulty in studying neurological symptoms in a pandemic, as fear, isolation and lockdowns due to the pandemic can lead to similar symptoms among the uninfected.

Taquet et al,[89] using data extracted from electronic health records of 236379 COVID-19 survivors, found an estimated incidence of a neurological or psychiatric diagnosis in the following 6 months to be 33.6%, while those with a new diagnosis were at 12.8%. Patients in intensive care units had 6-month incidence of diagnosis of 46.5% with 25.7% being a new diagnosis. Primary symptoms reported, with estimated incidence overall and ICU patients, were anxiety disorder (17.4%, 19.1% ICU), psychotic disorder (2.8%, 2.8% ICU), ischemic stroke (2.1%, 6.9% ICU), dementia (0.67%, 1.74% ICU), intracranial hemorrhage (0.56%, 2.7% ICU) and parkinsonism (0.11%, 0.26% ICU).

In a highly informative review, Nalbandian et al[90] summarized the current view of post-acute sequelae of COVID across organ systems. They review the neuropsychological sequelae and discuss the mechanistically diverse pathophysiology that potentially drives the symptoms, including immune dysregulation, inflammation, microvascular thrombi, iatrogenic medicine effects and psychosocial impacts.

**Future directions.** While the rapid publication of data pertaining to the neurological manifestations of COVID-19 have proven useful in our understanding of the pathobiology of the disease, there is still much to be learned. Severely affected patients were the focus of early studies and initial clinical trials of potential treatments, in part due to immediate logistics and ethical considerations. Many potentially promising studies were stopped for futility because treatments with anti-inflammatory or anti-coagulant therapies at late stages of COVID-19 were not effective.[91-96] Secondary analysis of some of these trials showed modest effects on those with less severe symptoms, indicating that treating earlier in the disease progression might prove more efficacious.[91]

The association of comorbidities, such as hypertension, diabetes and obesity, with disease severity has been striking, yet the biology contributing to this association is not understood. These comorbidities are related to damage to endothelium and there are many hypotheses about viral infiltration through damaged endothelium.[81] A better understanding on how the virus can translocate throughout the body is greatly lacking.

Additionally, other potential underlying conditions that might increase susceptibility to Sars-Cov2 or severity of infection are yet to be determined. This is where the ongoing NIH cohort studies, with extensive historic data, could add important information about pre-clinical states that might increase susceptibility. Studies like C4R (The Collaborative Cohort of Cohorts for COVID-19 Research),[97] a collaboration of 14 such studies that have historic data and stored specimens from over 50,000 multi-ethnic participants from across the United States, can add some information on susceptibility. These participants have consented to COVID-19 questionnaires and medical records extraction, as well as providing blood spots for serologic testing. Serologic testing for antibodies to both the spike protein and the nucleocapsid protein will distinguish between those exposed to the virus (nucleocapsid and spike antibodies) from those receiving a vaccination (spike antibodies only). These participants also have historic data (medical/family history, medications,

heart/lung/brain imaging, sleep studies, lung function testing, genomic, proteomic, metabolomic, neighborhood and social economic status, etc.) and stored samples (blood, urine). Many participants have been part of a study for over 20 years with yearly phone follow-up and multiple in-person visits. The current age range of participants is 18 to over 100. These studies have pre-pandemic data on cognitive function, sub-clinical/clinical atherosclerosis, lung function, heart/lung/brain imaging, genomic, proteomic, and metabolomic profiles that can provide insight into risk/susceptibility that cannot be ascertained from pandemic/post pandemic studies. As more information on potential biomarkers, particularly for route of entry markers such as endothelial dysfunction and blood brain barrier disruption, becomes available post-pandemic, the stored historic samples will prove useful in determining who becomes severely ill with COVID.

Similarly, Douand et al[98] recently examined brain MRI data obtained from the UK BioBank study of pre-COVID participant to a set of post-COVID participant data obtained in 401 COVID positive and 384 COVID negative participants. The positive participants, compared to the negatives, showed a more pronounce reduction in grey matter thickness and contrast in the lateral orbitofrontal cortex and para-hippocampal gyrus, an increase in diffusion indices, a marker of tissue damage, in the brain region that is functionally connected to the piriform cortex, anterior olfactory nucleus and olfactory tubercle, and reduced global measures of brain size with increased CSF volume. They also showed larger cognitive decline using the Trail making test. This is an excellent example of the value of pre-COVID measures in evaluating the effects of the virus.

Proal and VanElzakker[65] present potential mechanisms by which RNA viruses beyond just SARS-SoV-2 are connected to long-term health consequences. The development of long-term symptoms following viral and bacterial infections in a subset of patients has been well-documented.[99-107] SARS-CoV-2-associated long-term health effects appear new and novel mostly due to the relatively large number of people affected. Many of the ME/CFS patient symptoms are traced back to viral or bacterial infections. The overlapping symptoms between PASC and ME/CSF are reviewed extensively.[65] They also present potential mechanisms for PASC, as follows: direct consequence of SARS-CoV-2 infection of one or more organs, SARS-COV-2 immune dysregulation causing re-activation of latent neurotropic pathogens (ie Herpes viruses); SARS-CoV-2 alterations to the microbiome, coagulation system, brain stem/vagus nerve signaling, immune cell dysregulation and/or autoimmunity caused by molecular mimicry.[108] Data supporting these hypotheses is presented with mechanisms likely to overlap in any given individual.

To further support the notion of viral reservoirs in the body, a study by Kumata et al[109] developed a tissue level atlas of healthy human virome by performing a meta-transcriptomic analysis of RNA-sequencing data from 51 somatic tissues from 547 individuals. They found RNA from 39 viral species in various tissues. The Hu-COV-229E human coronavirus was found in brain, thyroid, lung, stomach, adrenal gland, skin, and blood, showing that reservoirs of the common coronavirus can be found in various tissues in the body. Whether this is true for SARS-CoV-2 has yet to be determined.

## CONCLUSIONS

Neurological manifestations of COVID-19 have been demonstrated using a variety of techniques. Some of the symptoms are acute while others are chronic. While case reports and autopsy studies gave us the first glimpse into the neurological manifestation in severe COVID-19 infections, the clinical labs analyzing blood and CSF gave us quantitative reports on organ function, coagulopathies, and remote infections, the radiologists gave us a look inside the brain for signs of damage and irregularities, the animal studies let us look at specific proteins, cells and organs with a platform for treatment testing, and the basic scientists looked at transcription changes, cell-specific COVID-19 alterations in immune response and testing models for potential treatments. Previous studies on other viruses gives us a starting point to understanding long-term health conditions associated with COVID-19. Ongoing cohort studies give access to pre-COVID-19 blood, urine and tissue samples, as well as imaging, comorbidity data, socio-economic status, and medical histories on a diverse population. Finding specific blood or CSF biomarkers that can discriminate COVID-19-specific pathophysiology from other disease or aging processes is essential to progressing the field. The combination of approaches should guide our understanding of PASC and hopefully guide treatments that will not only be affective in COVID-19 associated PASC, but potentially other infection-related post-infection neuropathies. It should also be noted that our notion of long-term consequences, at this point in time, is only ~2 years and the potential for longer term effects remains to be determined. The newly announced NIH RECOVER study,[110] which expects to enroll up to 40,000 participants to study post-acute sequelae of COVID should accelerate our understanding and hopefully find treatments.

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