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The pathogenesis of neurologic symptoms of the post-acute sequelae of SARS CoV-2 infection

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Abstract

Purpose of the review: The coronavirus disease 2019 (COVID) pandemic has resulted in significant mortality and morbidity globally. Patients who survive infection may develop continuing disease collectively known as the post-acute sequelae of SARS CoV-2 infection (PASC), which includes neurologic symptoms especially fatigue and cognitive impairment. The pathogenic mechanisms driving PASC are unknown although a post-infectious process, persistent infection, or lasting pathophysiological changes that occur during acute infection are all suspected to contribute.

Recent findings: Here we review the current evidence underlying potential pathogenic mechanisms of the neurological complications of PASC with particular emphasis on the evidence for post-infectious immune processes and viral persistence.

Summary: Immune dysregulation favoring persistent inflammation, including neuroinflammation and enhanced autoimmunity, are present in patients with COVID and likely contribute to the development of PASC. Limited evidence of viral persistence exists but may explain the ongoing inflammatory processes and affinity maturation observed in some patients recovering from COVID infections. No specific studies to date have tied persistent infection to PASC. CNS trauma, in particular hypoxic changes in the CNS, and psychiatric complications occur with greater frequency in patients with COVID and may contribute to the development of PASC. Future research is needed to fully understand the pathophysiological mechanisms driving PASC.

Keywords

SARS-CoV-2; post-acute sequelae of SARS CoV-2 infection; long-COVID; neurological impairments; autoimmune

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Introduction

The coronavirus disease 2019 (COVID) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in over five million deaths and 353 million infections [1]. Approximately 30% of patients develop continuing disease that impairs quality of life, collectively known as post-acute sequelae of SARS CoV-2 infection (PASC) or “long-haul COVID” [2]. PASC occurs even in patients with mild infections and is comprised of a spectrum of symptoms, including neurological manifestations such as fatigue and cognitive impairments which have resulted in disability and are creating a long-term health burden from this pandemic [3–5]. PASC is an important ongoing consequence of SARS-CoV-2, yet its cause(s) remains undefined. The spectrum of neurological symptoms associated with PASC may be due to a post-infectious process, a persistent infection, or from lasting pathophysiological changes that are initiated during acute infection. The goal of this review is to present the current evidence underlying these potential disease drivers with particular emphasis on the evidence for post-infectious processes and SARS-CoV-2 viral persistence.

It is important to acknowledge that patients with PASC are heterogeneous in their clinical presentation [4, 6–8] . PASC is likely not a single disease entity driven by a unifying disease process, but instead it is an umbrella term for a spectrum of complications that are associated with SARS-CoV-2. It is also important to acknowledge that there is much about COVID that remains unknown. This review therefore has many limitations, the most important being that the COVID pandemic has not ended and that our understanding of the virus and its physiologic impacts continues to evolve. As this manuscript is being prepared, the Omicron surge has begun, and we do not yet know if this variant will have similar phenotypes or rates of neurologic complications associated with it.

Neurologic complications associated with SARS-CoV-2

Persistent neurologic symptoms are the most frequently reported PASC complications. In the patient-led study that initially described long-haul symptoms, fatigue was overwhelmingly the most frequent complaint. Fatigue, body aches, difficulty concentrating, headaches, difficulty sleeping, anxiety, memory problems, and dizziness were nine of the top ten most frequently endorsed complaints [9]. These findings have been now replicated in multiple studies within the first month after COVID recovery [8, 10, 11] and a recent study shows that fatigue and cognitive dysfunction often continues to persist after six months [4].

The symptom complex in PASC is consistent with those previously described as the “postviral fatigue syndrome”. As initially described by Behan and Behan in 1984 [12], the postviral fatigue syndrome is an aversive constellation of symptoms where the “principle symptom is severe muscle fatiguability, but there may be a range of secondary symptoms, such as the aching of muscles, disequilibrium, and psychiatric manifestations.” Estimates of the incidence of postviral fatigue syndrome after viral meningitis, Epstein-Barr virus, and Ross River virus infections range between 10-12% [13, 14]. These persistent issues have also been reported as sequelae of other coronaviruses, including SARS and MERS [15].

There are other meaningful neurological complications from PASC. Peripheral neuropathies have been reported as sequela of COVID [16] and may be the consequence of COVID immune-mediated neuronal or vascular injury, medication toxicity, or compression injury [17]. Anosmia, parosmia, ageusia, and parageusia are also commonly reported PASC complications. It is currently thought that these neurological complications are caused by injury [18] of neuronal supportive cells and dysinnervation during healing.

Potential pathogenic mechanisms of PASC

As described, PASC includes neurologic complications unique from the acute disease phase. These symptoms may be due to immune mediated post-infectious processes, direct or indirect damage driven by chronic viral infection, or from stress, damage, and failed healing of injury sustained from the acute infection (Figure 1). Evidence exists for all these mechanisms to contribute to the development of PASC.

Immune mediated post-infectious processes

Recent work has revealed that immune dysregulation persists in patients who develop PASC as compared to patients who fully recover [19**, 20*]. Patients with PASC could be distinguished with a collection of proinflammatory biomarkers [19] and alterations in transcription in immune cells were detected in patients with PASC at 24 weeks post-infection [20]. Notably, increased gene transcription of cell cycle and translation were increased in patients with PASC and there was a robust decrease in platelet gene expression [20]. Importantly, there were no differences detected at earlier times points, suggesting that patients with PASC have ongoing gene expression alterations as compared to patients that recover. Alterations in neuroinflammation are also detected in patients with PASC. Within the CNS SARS-CoV-2 drives microglial activation, myelin loss, and increases CSF proinflammatory cytokines even in the absence of CNS infection [21**]. CCL11, which has been found to be correlated with impaired neurogenesis [22], was elevated in patients with PASC as compared to patients who fully recovered from infection. As both systemic and neuro-inflammation are associated with impaired cognition [23], these processes may be contributing to the neurologic complications observed in patients with PASC (Figure 1A).

SARS-CoV-2 also appears to increase the risk of development of autoimmunity. Multiple studies have demonstrated that patients with COVID develop autoantibodies at elevated levels as compared to uninfected controls [24–26]. Some of the immune specificities detected in SARS-CoV-2 patients are known autoantigens including La [27], Ro [28], ANA [24–26], and phospholipids [29, 30]. Although frank autoimmune encephalitis associated with COVID appears infrequent [31], antibodies associated with these conditions including NMDAR [32–34], CASPR2 [35], MOG [36, 37], and GAD65 [38] have been described in patients with COVID and neurological disease, many which responded to immunotherapy. A recent report of NMDAR encephalitis occurring in a patient post-COVID vaccination [39*] emphasizes that this process is immune mediated. In addition to anti-neuronal antibodies, antibodies that alter vasculature and thrombotic processes could both directly and indirectly impact the CNS and contribute to the development of PASC. Antibodies that inhibit the function of ACE2, the receptor for SARS-CoV-2, have been described in patients with

COVID and are associated with elevated levels of ANG II [40]. In addition to increasing blood pressure, ANG II can drive inflammation and neurodegeneration (reviewed in [41]). Antibodies to neutrophil extracellular traps (NETs) have been detected in patients with COVID [42, 43]. These antibodies appear to induce thrombosis by triggering the formation and impairing the clearance of NETs. Excessive presence of NETs is associated with the formation of blood clots (reviewed in [44]) which may increase the risk of stroke and neurological injury (see "Trauma and stress" section below) in patients with COVID [45]. However, to date, no studies have specifically looked at anti-neuronal, NETs, or ACE2 immune specificities in patients with PASC.

The few studies that have specifically examined autoantibodies in patients with PASC are suggestive that post-infectious autoimmune processes persist. In one cohort of 95 patients with PASC, 80% of the patients had autoantibodies 110 days after infection with SARS-CoV-2 and 40% of the patients had antibodies to two or more immune specificities [46*]. Another study of 31 patients, composed primarily of patients with neurological symptoms, found antibodies to β2 adrenoceptor, muscarinic M2 receptor, angiotensin II AT1 receptor, and angiotensin 1-7 MAS receptor [47*]. Antibodies to the β2 adrenoceptor and muscarinic receptors have been noted in subsets of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or Postural Orthostatic Tachycardia Syndrome (POTS) [48, 49]. The overlap of symptoms with ME/CFS and POTS, especially fatigue, suggests that infection-initiated immune-mediated dysregulation of nervous system receptors may have a causal role in a subset of patients with PASC.

Persistent virus

Another hypothesis is that PASC is due to persistent infection in a subset of patients, which in addition to direct viral damage, could drive chronic inflammation and immune-mediated tissue damage (Figure 1B). While most patients clear infectious virus within nine days, and viral RNA ceases to be detectable between 14-17 days [50, 51], emerging evidence suggests that subsets of patients could have persistent infection. Extended duration of viral RNA detectable in the respiratory tract and feces of several months has been described [50, 52–54], as have intermittent PCR negative and positive tests, including in patients with PASC [55–57]. However, without sequential viral sequencing it is unclear if this represents reinfection or reemergence of the original viral infection. Studies with such sequencing suggest both reinfection and chronic infection are possible.

In a large cohort of patients (n=133,266), two people were identified as having persistent infections with high titer virus that was sequenced and shown to be the same virus as the original infection at day 80 and 62 post original PCR [58]. In a group of 38 patients with long-term infection, defined as a positive PCR test for greater than four weeks, viral RNA was detectable in oral swabs and sputum samples that were analyzed weekly for six weeks [59]. In two of the sputum samples analyzed, infectious virus was cultured, representing viable virus 102 and 73 days after initial infection. Whole genome sequencing of the cultured virus demonstrated genomic alignment to virus circulating at the time of initial infection and repeated sequencing showed minimal or no genetic alterations, strongly suggesting persistent infection as compared to reinfection [59]. Yet in another

study, sequencing showed different lineage of virus from two people identified as having a second PCR positive test 108 and 126 days after infection, suggesting reinfection [55]. Collectively, sequential sequencing data suggests that although infrequent, both reinfection and persistent infection of replication competent virus can occur. Post-mortem studies also suggest that some patients may have chronic infections. Case reports and small studies have found that the virus can persist in the lung months after infection, despite clearance from other clinical samples such as the sputum or nasal secretions [60, 61**]. Importantly, in addition to virus being present in the lung, three patients that died between day 19 and 43 of disease had detectable spike protein in subsets of neurons in the CNS, indicating that neuronal infection with SARS-CoV-2 can occur [61]. However, the frequency in which virus invades or persists in the brain remains unclear, as is the direct contribution of CNS infection on the development of PASC [62].

Studies evaluating ongoing immune response evolution also suggest that SARS-CoV-2 can persist. In one study, immune responses from 87 patients were examined one and six-months after infection. While no patients were PCR positive at the six-month time point, there was ongoing IgA affinity maturation [63*]. As this process requires antigen the authors collected biopsies from the GI tract of 14 individuals, five of which showed viral antigen by immunofluorescence, confirmed to be SARS-CoV-2 by sequencing [63]. This suggests that virus can persist in some body compartments and continue to drive immune responses. Similar antiviral IgA kinetics were observed in a study that monitored antibody titers for 14 months in 278 people infected with SARS-CoV-2 with mild disease [64]. While virus was not detected by PCR, IgA levels continued to rise steadily in a subset of patients, suggesting ongoing immune stimulation [64]. In another study of 203 post-symptomatic patients, the majority of which had mild illness, 5% of patients were PCR positive greater than 90 days post infection and a subset of these patients had high viral loads, similar to those observed during acute infections [65*, 66]. Further characterization of the immune response in these patients revealed increased levels of viral specific CD8+ T cells that recognized more epitopes as compared to patients without a PCR positive test at 90 days [65]. Collectively these studies suggest that in a subset of patients recovering from viral infection there is ongoing viral replication that results in continued immune system stimulation. However, no studies to date have examined extended viral persistence and continued immune evolution on the development of PASC.

While there is not a consensus on persistent SARS-CoV-2 infections, it is important to note that the formation of cell-free replication competent virions is not a requirement for viruses to drive CNS pathologies or establish chronic CNS infections. For example, measles and other viruses (reviewed in [67]) can persist in the CNS and spread via cell-to-cell contact by various mechanisms. Importantly, neutralizing antibodies are not able to reduce viral transmission and there is a reduction in the ability of virus to be detected in fluids such as the CSF as cell free viral particles are not released [68–71]. While SARS-CoV-2 does appear to infect the CNS of a subset of patients, we do not currently know if SARS-CoV-2 establishes a reservoir in the CNS. Although case reports of viral RNA detected in the CSF of patients with PASC have been published [72], no systematic evaluation of CSF samples from a large set of patients has thus far shed light on this issue.

Trauma and stress

The neurologic complications observed in patients with PASC could also arise from permanent damage and neuronal reorganization sustained by the CNS during acute infection (Figure 1C). One of the major risks to the CNS from SARS-CoV-2 is ischemic stroke, which is greatly elevated in patients with COVID as compared to other viral infections [73]. While the risk of thrombosis appears to increase with COVID disease severity (reviewed in [74]), a quarter of the patients in a retrospective study presenting to the emergency room for stroke were found to have COVID [73], suggesting that stroke can occur even in patients not requiring hospitalization for their SARS-CoV-2 infection. An additional study examining asymptomatic male patients who were younger than 50 years of age further confirmed that there is an increased risk of stroke after COVID, with the mean time to stroke event being 54 days post infection [75]. Further, a post-mortem series demonstrated microvascular damage in the CNS of patients including non-hospitalized COVID patients that died suddenly [62*]. Here the authors demonstrated that abnormalities on MRI represented thinning of the basal lamina of the endothelial layer with corresponding fibrinogen leakage into the CNS [62]. While no patients in this series had PASC, persistent endothelial dysfunction has been linked to PASC [76] and this series suggests that endothelial dysfunction occurs even in those not requiring hospitalization. Other post-mortem series have also described hypoxic changes and vascular damage in the CNS [77] and these concur with MRI studies demonstrating that patients with neurologic symptoms have imaging results consistent with infarcts, hemorrhage, or global hypoxic ischemic encephalopathy [78].

It is notable that cognitive deficits [79] and chronic headaches [80] are both common complications in patients recovering from mild ischemic stroke and those with PASC. Vascular damage leading to permanent CNS tissue damage can occur in the wake of even mild ischemic events. Beyond the direct tissue damage, neural repair after stroke involves multiple integrated processes with changes in both structure and function. There is a substantial amount of personal variation in this recovery that belies variation in genetics, environment, and behavior [81]. It seems likely that the vasculopathy of COVID contributes to the development of PASC symptoms in some patients.

Another contributor to PASC may be stress and psychological trauma. It has been demonstrated that post-intensive care syndrome (PICS), which include neurological complications such as post-traumatic stress disorder, depression, neuromuscular weakness, chronic inflammation, and cognitive impairments, occurs frequently in patients with COVID and that COVID is associated with elevated rates of depression even in mild cases not requiring hospitalization [82, 83]. Further, patients with COVID with new onset depression or adjustment disorders show elevated levels of systemic inflammation [84]. As patients with stress-related disorders, such as PICS, are at an increased risk of developing autoimmune diseases [85], it is important to consider that the outlined potential pathogenic mechanisms are not independent from each other but may overlap and fuel other mechanisms driving the neurological manifestations of PASC. Stress, ischemic events, and chronic infections are all proinflammatory and can drive immune mediated damage to the CNS. In turn, chronic inflammation is a risk factor for thrombotic events such as stroke [86] and can contribute to neurocognitive impairments and neurodegeneration [87, 88].

Conclusions

PASC is an important complication of SARS-CoV-2 infection and currently we are not able to predict who will develop long-term complications, if they will persist or resolve, or if PASC is preventable. A barrier to these advancements is that patients with PASC may have very different disease processes despite similarities in clinical phenotype. In this review we suggest that the neurologic manifestations of PASC are driven by multiple mechanisms including immune-mediated processes, chronic viral infection, and trauma and stress. It is important for future research to take these processes into consideration and to group patients, by deeply phenotyping them, into biotypes based on pathogenic processes as the prognosis and therapeutic avenues for patients with PASC will likely differ among these groups. The phenotyping should include neurological and psychological evaluations to understand the confluence of these processes on the development and persistence of PASC. Further, the development of biomarkers for chronic inflammation, including neuroinflammation, may identify patients that would benefit from immune suppressive therapies. Additional studies are needed to determine if chronic infection with SARS-CoV-2 occurs and if so, where the relevant reservoirs of virus reside and how these potential reservoirs might be eliminated.

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Key points

- Neurologic complications are common features of PASC.
- Multiple disease mechanisms including chronic infection, post-infectious immune processes, hypoxic CNS injury, and stress may contribute to PASC development.
- PASC is heterogeneous in cause and will require clinicians and researchers to consider these potential mechanisms as patients are evaluated to avoid misclassification and treatment errors.
- Grouping patients with PASC into biotypes based on pathogenesis may help elucidate therapeutic avenues.

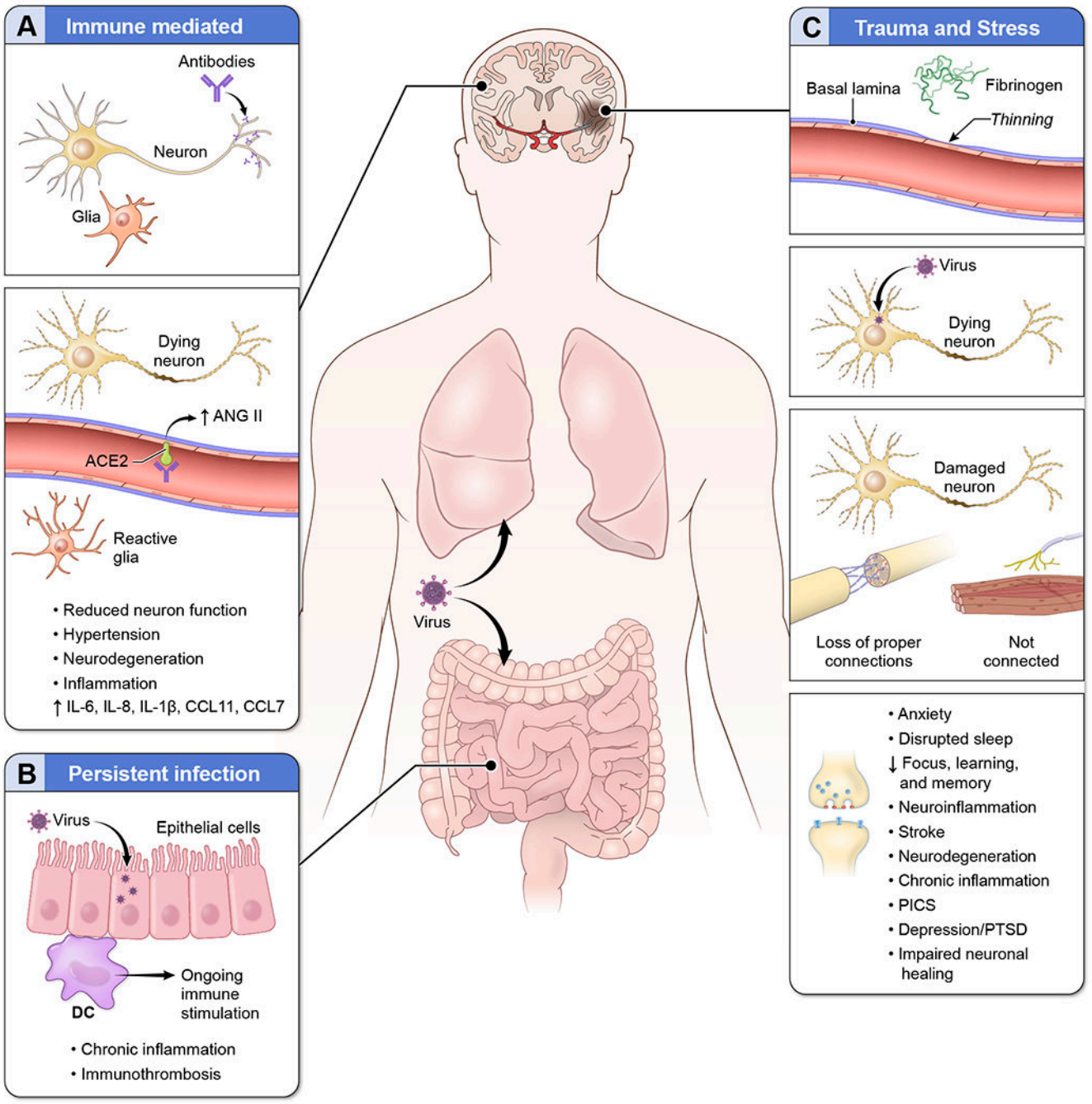

Figure 1. Potential pathogenesis of neurologic complications observed in patients with PASC.

Multiple pathogenic mechanisms likely contribute to the development of neurologic complications in patients with PASC including (A) immune mediated processes. Antibodies that specifically target neuronal proteins have been detected in patients with COVID. These antibodies can impair neurologic function, induce neurodegeneration, and trigger proinflammatory processes within the CNS. Antibodies that recognize ACE2 on endothelial cells can inhibit enzyme function leading to increased levels of ANG II in the CNS, which in turn can drive neurodegeneration and neuroinflammation. Elevated neuroinflammation,

including reactive glial cells and increased proinflammatory cytokines, has been observed in patients with SARS-CoV-2 infection even in the absence of virus in the brain. (B) Persistent infection may also contribute to the development of PASC. In some patients, virus appears to persist in the lung and GI tract. The virus in these compartments can cause ongoing immune stimulation and persistent inflammation. Systemic inflammation is associated with cognitive impairments including executive function and memory. Chronic inflammation is also associated with the development of thrombi which can increase the risk of stroke and drive further inflammation. (C) Trauma and stress may also contribute to the development of PASC. Stroke and hemorrhage into the CNS occur in patients with COVID resulting in CNS tissue destruction and neuronal loss. Microvascular damage and associated hypoxia induced changes can also result in neurodegeneration and promote neuroinflammation. Direct infection of the CNS has been reported, including in neurons, which can also contribute to neurodegeneration. In neurons that have been damaged, repair processes may also be impaired resulting in loss of proper connections or in neurons that do not fully re-connect to innervated tissues. Lack of proper healing may also contribute to the development of neurological symptoms in PACS. Depression, anxiety, post-traumatic stress disorder, and PICS can also directly contribute to suppression synaptic receptors and CNS function resulting in impairments in focus, learning and memory.