CME

Post-COVID-19 neurologic syndrome: Another legacy of the pandemic

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ABSTRACT

COVID-19 quickly escalated to a global pandemic in 2020. As research on the topic continues, the medical community has found that this acute illness can cause a new chronic illness: postacute sequelae of SARS-CoV-2 (PASC). Some patients with PASC develop predominately neurologic sequelae (post-COVID-19 neurologic syndrome or PCNS). This article describes PASC and PCNS, their proposed pathogenicity and possible neurovirulence mechanisms, symptoms, and treatment recommendations.

Keywords: postacute sequelae of SARS-CoV-2, PASC, post-COVID-19 neurologic syndrome, PCNS, COVID-19, long COVID, SARS-CoV-2

Learning objectives

- Identify the proposed neurologic pathogenicity mechanisms of SARS-CoV-2.
- Recognize the most common symptoms of two new, emerging conditions, PCNS and PASC.
- Review treatments for PCNS and PASC.

COVID-19, caused by SARS-CoV-2, emerged as a novel, predominately respiratory illness in Wuhan, China, in December 2019. This illness quickly escalated to a global pandemic in 2020. As of June 2022, more than 540 million cases and 6.3 million deaths have been confirmed globally.[1] In a subset of patients who survive the acute phase of COVID-19, a vast array of lingering symptoms may persist for variable amounts of time, including after the acute phase of the illness.[2]

One study found that more than 87% of patients suffered from at least one symptom 2 months after their COVID-19 symptomatic onset.[3] The risk of developing these symptoms is not thought to be correlated with the severity of the acute phase of COVID-19, making even mild or asymptomatic cases susceptible to persistent symptoms.[3]

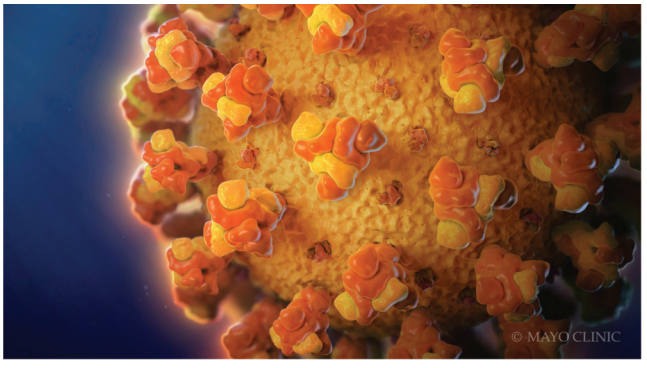

FIGURE 1. SARS-CoV-2
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At present, this condition has no established terminology; several names are used interchangeably in the literature, including long COVID-19, long-term COVID-19 effects, postacute COVID-19 syndrome, post-COVID-19 syndrome, long haulers, persistent COVID-19 symptoms, and post-COVID-19 manifestations.[4] Recently, the National Institutes of Health (NIH) started to use postacute sequelae of SARS-CoV-2 (PASC) as a term to describe this condition.[5] Some patients develop predominately neurologic symptoms following their COVID-19 illness, leading to publications describing this symptomatology as post-COVID-19 neurologic syndrome (PCNS).[6] This article uses PCNS to describe the neurologic symptoms that can follow an infection from SARS-CoV-2.

With more than 440 million confirmed cases of COVID-19 globally, the affected public now could be suffering from two new chronic clinical entities: PASC and PCNS. This article describes how to identify PCNS as a subset of PASC, and how to best manage these novel conditions.

PATHOGENESIS AND NEUROVIRULENCE

SARS-CoV-2 is a single-stranded RNA virus that is responsible for causing COVID-19 (**Figure 1**). Whole genome

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Key points

- PASC is a new condition that can develop in any patient following a COVID-19 diagnosis, regardless of initial COVID-19 severity.
- PCNS is a subset of PASC, consisting predominantly of neurologic symptoms following a COVID-19 diagnosis.
- Treatment for PASC and PCNS often requires a multidisciplinary approach and should be individualized to patient needs.

sequencing of SARS-CoV-2 was submitted on January 17, 2020, to the National Center for Biotechnology Information (NCBI) database, revealing a 29,903 base pair genome.[7] It is the seventh known coronavirus that can infect humans.[8] Originally, SARS-CoV-2 was thought to cause mostly pulmonary disease. However, research and experience have found that this virus can cause multisystem disease, and several mechanisms have been proposed for its neurovirulent potential.

One hypothesis is that SARS-CoV-2 enters the brain through the olfactory nerve.[9] The virus is known to use the angiotensin-converting enzyme 2 (ACE2) receptor for entry into host cells. ACE2 receptor expression is present in several organs throughout the human body, and recent studies have found evidence of ACE2 receptor protein expression in human neurons.[10] Because the olfactory epithelium has been found to express the ACE2 receptor, and is near olfactory neurons, some authors think that this could be a direct pathway into the human brain.[9] However, new evidence suggests that the virus may use another mechanism to travel from the nose to the brain, because olfactory receptor neurons lack the expression of, or only rarely express, the ACE2 receptor.[11] Once in the brain, SARS-CoV-2 is thought to transfer from neuron to neuron in a trans-synaptic fashion because of the expression of the ACE2 receptor on neuronal membranes.[9] Another membrane protein, neuropilin-1, also has been implicated in the potentiation of SARS-CoV-2 infection in neural tissue.[12]

Another hypothesis is that the virus crosses the blood-brain barrier. Vascular endothelial cells control the permeability of the blood-brain barrier via tight junctions (**Figure 2**). However, endothelial cells are also known to express the ACE2 receptor, which can lead to virus-induced disruption of the tight junctions and allow passage of SARS-CoV-2 through the blood-brain barrier.[13] Electron microscopy has confirmed the binding of SARS-CoV-2 to ACE2 receptors on vascular endothelial cells. After successful binding, the virus was shown to enter the cell by endocytosis and transfer to neighboring cells via exocytosis.[9] A separate postmortem case report used transmission electron microscopy on brain tissue from a patient with confirmed SARS-CoV-2 infection and found evidence of viral particles coming out of endothelial cell walls.[14]

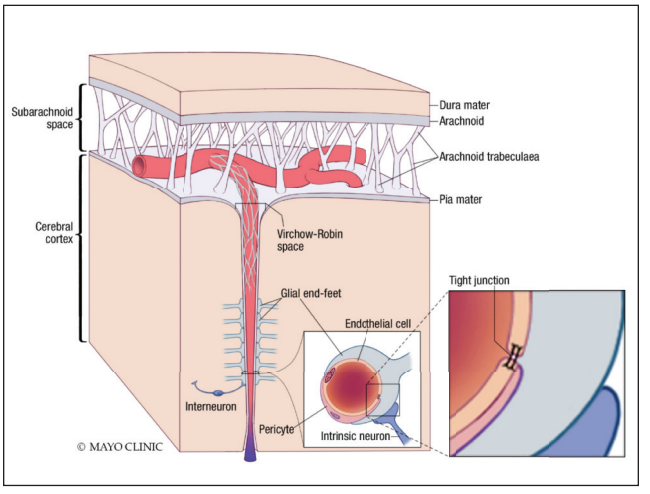

FIGURE 2. The neurovascular unit

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Another possible mechanism for SARS-CoV-2 to cross the blood-brain barrier, in addition to passing through vascular endothelial cells, is if it uses immune cells as a Trojan horse. Lymphocytes, granulocytes, and monocytes are also known to express ACE2 receptors. SARS-CoV-2 could bind to these cells and migrate via the bloodstream, possibly crossing the blood-brain barrier.[15] This mechanism already is well established in HIV, in which infected immune cells can travel from the patient's circulation and cross the blood-brain barrier to infect the central nervous system.[16] This proposed mechanism may explain why some patients with a robust immunologic response (such as those with chronic obstructive lung disease or heart failure) are at high risk for COVID-19: they have increased numbers of alveolar monocytes and macrophages in bronchoalveolar lavage specimens.[17] These alveolar monocytes and macrophages serve as a first-line defense against SARS-CoV-2, and some of these cells may act as a viral reservoir, propagating the disease via the Trojan horse mechanism.[17]

Once SARS-CoV-2 is in the body, it induces a robust innate immune response that leads to systemic inflammation.[9] Considering this degree of inflammation, one study mentions the possibility of Epstein-Barr virus (EBV) reactivation as a mechanism for these symptoms.[18] An estimated 90% of adults have antibodies that indicate previous infection with EBV.[18] A study published in *Pathogens* found that 66.7% of patients with "long COVID" also were positive for EBV reactivation.[18] The study authors concluded that symptoms following COVID-19 might be caused by the virus reactivating EBV.[18]

The robust systemic inflammation caused by COVID-19 also may lead to cerebrovascular damage and multiorgan dysfunction.[19] COVID-19 can cause acute ischemic stroke because of the shared pathophysiologic mechanisms between these two conditions.[19] The cascade begins with

the binding of SARS-CoV-2 to the ACE2 receptors on lung alveolar pneumocytes. This leads to a viral infectious process that affects many other cells throughout the body. A large inflammatory process then ensues, leading to the release of von Willebrand factor and increased platelet aggregation. This can lead to thromboembolisms and disruption of the blood-brain barrier. Subsequently, hypoperfusion of cerebral tissue can follow, causing an acute ischemic stroke.[19]

DIAGNOSIS AND RISK FACTORS

No test can definitively diagnose PASC or PCNS, therefore the diagnosis is largely clinical.[20] Consider the patient's history, physical examination, symptoms, and duration of symptoms. There is no consensus for how long symptoms should be present in order to establish the diagnosis.[3] According to the CDC, patients with symptoms persisting 4 or more weeks after SARS-CoV-2 infection can be considered as having "post-COVID conditions," a broad term that would encompass PASC and PCNS.[21] The patient's symptoms must not be explained by an alternative diagnosis, SARS-CoV-2 reinfection, or the unmasking of a preexisting health condition.[21] Recently, the World Health Organization (WHO) led a Delphi process in which 265 international panelists met to develop a global consensus definition for PASC.[22] The consensus definition reached for adults with this condition included patients "with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis."[22]

Risk factors for PASC are under investigation. A longitudinal study found that the presence of some biomarkers measured at the beginning of acute COVID-19 illness may predict the symptoms and type that PASC patients could experience after their acute disease.[23] Participants were found to be more likely to have PASC symptoms if they had type 2 diabetes, reactivation of latent EBV, circulating mRNA fragments of SARS-CoV-2 (RNAemia), or detectible autoantibodies akin to systemic lupus erythematosus autoantibodies.[23] The degree of inflammation from the acute phase of COVID-19 seems to be positively correlated with PCNS severity.[24] However "long COVID" can develop after COVID-19, regardless of disease severity or patient age.[4]

COMMON SYMPTOMS OF PASC

The postacute symptoms that follow a SARS-CoV-2 infection are broad and can differ based on the timing of the disease. A systematic review and meta-analysis described more than 50 long-term effects of COVID-19.[25] Fatigue was reported to be the most common symptom of post-COVID-19 syndrome at 100 days postsymptom onset.[25] Of patients with a confirmed COVID-19 diagnosis, 80% reported experiencing one or more symptoms 3 weeks after their acute illness began.[25] An international study of 3,762 patients sought to characterize the other most common symptoms that can manifest in PASC.[2] The study tracked patients' reported PASC symptoms over 7 months and found that the probability of symptoms lasting beyond 35 weeks was 91.8%, with a 95% CI (89.5%-93.5%) (**Table 1**).[2]

TABLE 1. Most common reported PASC symptoms from 3,762 participants in an online international survey with 95% CIs[2]

- **Systemic**—fatigue (98%), postexertional malaise (89%)
- **HEENT**—sore throat (60%), blurred vision (36%)
- **Respiratory**—shortness of breath (77%), dry cough (66%), episodes of breathing difficulties/gasping for air with normal SpO_2 (60%)
- **Cardiovascular**—palpitations (67%), tachycardia (61%)
- **Gastrointestinal**—diarrhea (60%), loss of appetite (52%), nausea (48%)
- **Reproductive, genitourinary, and endocrine**—irregular menses (26%), heavy menses (20%)
- **Musculoskeletal**—chest tightness (75%), myalgia (69%), arthralgia (52%)
- **Skin**—rash (28%)
- **Immunologic**—heightened reaction to old allergies (12%)

The NIH launched its REsearching COVID to Enhance Recovery (RECOVER) Initiative to investigate why some patients experience persistent symptoms beyond acute COVID-19 illness.[26] The study population of adults and children also will include pregnant patients, to help gain insight for ways to prevent and treat PASC.[26]

The symptoms of "long COVID" may mimic another condition known as myalgic encephalomyelitis/chronic fatigue syndrome. That condition is characterized by at least 6 months of subjective fatigue and exhaustion, or symptoms such as myalgia, cognitive impairment, and sleep impairment.[3,27] Although the duration of symptoms for "long COVID" has not been defined, patients whose symptoms persist 6 months or longer may meet criteria for myalgic encephalomyelitis/chronic fatigue syndrome.[3] One study compared the symptoms reported in a publication on "long COVID" to the 29 known symptoms of myalgic encephalomyelitis/chronic fatigue syndrome. That study found that 25 of 29 symptoms of myalgic encephalomyelitis/chronic fatigue syndrome were reported.[3] If myalgic encephalomyelitis/chronic fatigue syndrome does overlap with "long COVID," existing research on myalgic encephalomyelitis/chronic fatigue syndrome may benefit patients with "long COVID".[3] Symptoms of "long COVID" also are correlated with postural orthostatic tachycardia syndrome (POTS), but approaches for patients with "long COVID" could differ for those with predominately POTS symptoms versus those with predominately myalgic encephalomyelitis/chronic fatigue syndrome symptoms.[4]

SYMPTOMS OF PCNS

Some patients experience mostly neurologic symptoms following SARS-CoV-2 infection (**Table 2**).[2] *Brain fog* is a common term used by patients with this syndrome. The feeling of brain fog is characterized by fatigue, difficulties with concentration, memory impairment, and negative effects on cognition.[28] In patients recovering from COVID-19, cognitive abnormalities, such as slowed cognitive processing speeds and memory impairment, can persist months after the patients have been discharged from the hospital.[29] This altered cognition could interfere with patients' functional abilities and impede their return to work.[29]

A case report recently described a patient hospitalized with acute stroke-like symptoms.[30] These symptoms were later determined to be due to significant inflammatory injury to the brain, which raised intracranial pressure, causing transient cerebral edema and a hypoperfusion state. Signs of a stroke were not identified in this patient.[30] When discharged, the patient showed signs of PCNS. The patient was followed over 4 months and had serial systemic immune inflammation indices (SSIIi) drawn regularly. This laboratory test uses neutrophil, platelet, and lymphocyte counts. Each peak in the patient's SSIIi correlated with a neurologic event. The study authors postulate that SSIIi may serve as a useful prognostic biomarker for patients with PCNS.[24]

The robust systemic inflammation caused by COVID-19 also has been associated with rare cases of transverse myelitis.[31] The onset, which may either be acute or subacute, is due to spinal cord inflammation. Signs of transverse myelitis include paraplegia, quadriplegia, bowel and bladder dysfunction, and absent deep tendon reflexes.[31]

The causes of the neurologic symptoms for PCNS likely are due to an interplay of the pathogenicity and neurovirulence mechanisms discussed previously: direct viral invasion of the CNS, systemic inflammation, cerebrovascular changes, and organ dysfunction. These mechanisms reportedly put COVID-19 survivors at risk for developing long-term neurologic consequences. An article published in *Alzheimer's Research & Therapy* stated that systemic inflammation is known to promote cognitive decline and neurodegenerative disease.[32] COVID-19 survivors could experience neurodegeneration in the years following their illness because of systemic inflammatory damage to the brain.[32] This theory parallels the intense inflammation associated with the development of sepsis-associated encephalopathy. In a subset of these recovered patients, neurocognitive deficits can be seen years after their recovery.[33] Thus, COVID-19 survivors who experience a severe innate immune response may be at increased risk for developing Alzheimer disease.[32]

TABLE 2. Most common reported PCNS symptoms by 3,762 participants from an online international survey with 95% CIs[2]

- **Cognitive**—brain fog (85%), difficulty thinking (65%)
- **Memory**—short-term memory loss (65%), long-term memory loss (36%)
- **Speech and language**—difficulty with word finding (46%), difficulty communicating verbally (29%)
- **Sensorimotor**—dizziness, vertigo, unsteadiness, or balance issues (67%), paresthesias (49%), vibrating sensations (43%), tremors (40%)
- **Sleep**—insomnia (69%), waking up several times during the night (48%)
- **Headaches**—all types of headaches (77%)
- **Emotion and mood**—anxiety (58%), irritability (51%), depression (47%)
- **Taste and smell**—loss of smell (36%), loss of taste (34%)
- **Hallucinations**—visual hallucinations (10%)

TREATMENT

Treatment options for patients with PCNS parallel those for patients with PASC. No medications have been shown to be helpful with the symptoms of "long COVID" in large-scale studies.[4] However, research is underway into possible therapeutic options.

A multidisciplinary approach is one recommendation for treating patients who experience fatigue as part of their post-COVID-19 symptoms. Some other therapeutic interventions that have been proposed include structured exercise therapy, cognitive behavioral therapy, and input from occupational medicine providers to help patients return to work at an appropriate pace.[34]

Personalized rehabilitation programs are among the mainstays of treatment for patients with PASC.[4] Rehabilitation programs must be tailored to each patient in order to address their specific needs, as symptoms may vary among patients.[4] Cognitive rehabilitation therapy (CRT) may be indicated for patients with persistent cognitive symptoms or "brain fog" and can enhance processing speed and memory.[29] CRT, which is tailored to patients' needs, seeks to restore previous cognitive processes or use compensatory strategies to help patients regain their previous functioning.[35]

Persistent smell and taste dysfunction may be complications of a SARS-CoV-2 infection. A study of 111 patients with confirmed COVID-19 tested chemosensory dysfunction (isolated smell, taste, or combined dysfunction) during and after an acute COVID-19 illness (mean PCR test date 62.9 days after symptom onset).[36] Researchers found that most participants regained their senses of smell and taste within 28 days without treatment. However, a quarter of participants still experienced hyposmia or hypogeusia at follow-up, and the authors recommended that these patients be referred for chemosensory function rehabilitation.[36] Topical corticosteroids have been investigated as a potentially therapeutic, but high-quality evidence is lacking to support this practice routinely. For patients who do not

experience spontaneous improvement, olfactory rehabilitation is the only evidence-based treatment for patients with persistent postinfectious smell and taste disturbance.[37] Repeated stimulation of olfactory neurons with clearly defined odorants is thought to increase the olfactory system's regenerative and neuroplastic potential.[37]

A recent meta-analysis assessed the effect of statin medications on COVID-19 clinical outcomes in 8,990 patients.[38] Patients treated with statins had a 30% reduction in fatal or severe COVID-19. The benefit of statins appears to be a class effect and is thought to be due to the known inhibition of myeloid differentiation primary response protein (MYD88), thereby subduing intense inflammatory responses.[38] The Statin TReatment for COVID-19 to Optimise NeuroloGical recovERy (STRONGER) trial is now further investigating if this benefit applies to patients with PCNS.[39] The trial seeks to determine whether 40 mg of atorvastatin daily can improve neurocognitive function in adults with "long COVID" neurologic symptoms.[39]

Ultimately, prevention may be the best treatment; a recent study published in *Lancet Infectious Diseases* evaluated the risk of developing "long COVID-19" after receiving two doses of a COVID-19 vaccine (Pfizer-BioNTech, Moderna, or Oxford-AstraZeneca).[40] The study was conducted from December 2020 to July 2021 and found that the odds of having "long COVID" symptoms 4 weeks or more after infection with SARS-CoV-2 were reduced nearly in half compared with unvaccinated controls, with an odds ratio of 0.51 with a 95% CI (0.32-0.82).[40]

INEQUITIES

As PCNS continues to reveal itself as a novel, complex, poorly understood condition in industrialized countries, marginalized communities are experiencing a disproportionate burden because of global healthcare inequities. Underserved communities have poor access to SARS-CoV-2 testing, multidisciplinary centers, diagnostic modalities such as brain imaging, routine follow-up care, and rehabilitation programs.[41] Collectively, the pandemic has exacerbated existing healthcare inequities.[41]

CONCLUSION

PASC is becoming increasingly prevalent and is estimated to affect 5 million patients globally.[4] To better understand the growing needs of this condition and its neurologic subset, PCNS, the research community needs to become more unified on PCNS consensus terminology and definitions so that new research can be reproducible and easily communicated in the literature. Concrete diagnostic criteria, such as duration of symptoms, need to be established for PCNS. Lastly, more research is needed on PASC and PCNS to further understand the intricacies of these conditions and their long-term effects. The framework laid by the NIH's RECOVER Initiative provides hope that we will harness more and better information on how to prevent and treat these debilitating conditions as the pandemic continues to unfold. **JAAPA**

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