



A Disease Hidden in Plain Sight: Pathways and Mechanisms of Neurological Complications of Post-acute Sequelae of COVID-19 (NC-PASC)

Apoorva Saxena¹ · Josef Mautner²

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Abstract

The global impact of coronavirus disease 2019 (COVID-19) marked by numerous pandemic peaks is attributed to its high variability and infectious nature, transforming it into a persistent global public health concern. With hundreds of millions of cases reported globally, the illness is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite its initial classification as an acute respiratory illness, recent evidence indicates that lingering effects on various bodily systems, such as cardiovascular, pulmonary, nervous, gastrointestinal (GI), and musculoskeletal, may endure well beyond the acute phase. These persistent manifestations following COVID-19, commonly known as long COVID, have the potential to affect individuals across the entire range of illness severity, with a tendency to be more prevalent in mild to moderate cases. At present, there are no established criteria for diagnosing long COVID. Nonetheless, it is conceptualized as a multi-organ disorder encompassing a diverse array of clinical manifestations. The most common, persistent, and debilitating symptoms of long COVID may be neurological, known as neurological complications of post-acute sequelae of COVID-19 (NC-PASC). More than one-third of individuals with a prior SARS-CoV-2 infection show involvement of both the central nervous system (CNS) and peripheral nervous system (PNS), as evidenced by an approximately threefold higher incidence of neurological symptoms in observational studies. The persistent neurological symptoms of long COVID encompass fatigue, headache, cognitive decline, “brain fog”, dysautonomia, neuropsychiatric issues, loss of smell (anosmia), loss of taste (ageusia), and peripheral nerve problems (peripheral neuropathy). Reported pathogenic mechanisms encompass viral persistence and neuro-invasion by SARS-CoV-2, neuroinflammation, autoimmunity, coagulopathy, and endotheliopathy. Raising awareness of potential complications is crucial for preventing and alleviating the long-term effects of long COVID and enhancing the prognosis for affected patients. This review explores the hypothetical pathophysiological mechanisms and pathways of NC-PASC with a sole aim to increase awareness about this crippling disease.

Keywords COVID-19 · SARS-CoV-2 · Long COVID · NC-PASC · Neurological symptoms · Pathophysiological mechanisms

Introduction

The term long COVID was first coined by a patient and subsequently made public by Dr. Elisa Perego, an Italian scientist from University College London (UCL), on social media, to describe the enduring presence of symptoms for weeks or months after the initial infection with the virus [1, 2]. Since then, various terms such as post-COVID-19 syndrome, post-acute sequelae of COVID-19 (PASC), chronic COVID, and long-haul COVID have been used to describe the condition [3]. According to the WHO, long COVID is defined as the “continuation of symptoms or development of new symptoms 3 months after the initial SARS-CoV-2

✉ Apoorva Saxena
apoorva.saxena@campus.lmu.de

Josef Mautner
mautner@helmholtz-muenchen.de

¹ Department of Biology, Ludwig-Maximilians-Universität München, Munich, Germany

² Institute of Virology, Helmholtz Zentrum München, Munich, Germany

infection, with these symptoms lasting for at least 2 months with no other explanation. CDC uses the term “Post-COVID Conditions” (PCC) as an umbrella term for the wide range of symptoms that persist 4 weeks after infection, even if the recovery period is between 4 and 12 weeks. Different terms proposed by various organizations along with their definition and description of timelines are listed in Table 1. These terms may be used interchangeably to represent the term long COVID.

In 2023, approximately 65 million people around the world were suffering from long COVID [5]. Most of them were PCR negative, indicating microbiological recovery. Hence, long COVID is the time lag between microbiological recovery and clinical recovery. Long COVID is associated with all ages and acute phase disease severities, with the highest percentage of diagnoses between the ages of 36 and 50 years, and most long COVID cases are in non-hospitalized patients with a mild acute illness [5]. The risk of long COVID is more in women than men [5]. A single explanation as to why women are at higher risk is currently not available; however, the role of hormonal dysregulation has been proposed. In addition, autoimmunity may also be another reason and women are more prone to autoimmune diseases [6]. Male patients, however, show higher mortality rate after COVID-19 infection. The condition can be continuous or relapsing and remitting in nature [7].

In a study published in 2023, it was found that participants infected with the Omicron variant had the lowest risk of developing PCC, followed by Delta, Alpha, and Wildtype strains [8]. Furthermore, no variance in symptom severity among individuals developing PCC was noted, regardless of the variant, vaccination status, or prior infection [8]. Likewise, people infected with the Omicron variant had

a reduced risk of developing PCC, compared with Delta, Alpha, and Wildtype in a population-based cohort study in Sweden [9]. This is also in line with the findings from a case study in the UK, reporting 4.5% cases and 10.8% cases with PCC following Omicron and Delta virus infection, respectively [10]. Another study also identified three main phenotypes of PCC encompassing central neurological symptoms, cardiorespiratory symptoms, and systemic inflammatory symptoms that were consistently found across different variants (Alpha, Delta, and Wildtype) [11]. In addition, no significant differences in prevalence and duration of symptoms were noted between unvaccinated people who developed PCC from SARS-CoV-2 (either Alpha or Delta variant) and vaccinated people [11].

More than 200 symptoms have been identified with impacts on multiple organ systems [5]. The commonly reported symptoms are fatigue, myalgia, dyspnea, joint pain, chest pain, cough, headache, diarrhea, heart palpitations, skin rashes, and “pins and needles” sensation. In addition, inability to do routine activities leading to worsened quality of life, mental health issues like anxiety, and depression were also reported [3]. A summary of clinical manifestations during post-COVID-19 syndrome is listed (Table 2).

As listed in Table 2, long COVID can have a profound impact on multiple organ systems with varied manifestations. Hence, various pathophysiological mechanisms may exist that can contribute to this syndrome. One of the challenges in the diagnosis and management of long COVID is the overlapping of symptoms among organ systems. In addition, long COVID also has similarities with other chronic diseases like myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS). Currently, there are quite a few articles

Table 1 Different terms of long COVID along with their timelines [4]

Organization	Terminology	Proposed definition
WHO	Post-COVID	Condition arises in individuals with documented history of probable or confirmed SARS-CoV-2 infection, typically occurring around 3 months after the onset of COVID-19 symptoms; persist for at least 2 months and cannot be attributed to another diagnosis; symptoms may be newly developed or persistent
National Institute of Health (NIH)	PASC	Symptoms persisting beyond 4 weeks from the initial onset of COVID-19 symptoms
The National Institute for Health and Care Excellence (NICE)	Ongoing symptomatic COVID-19	Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks
	Post-COVID-19 syndrome	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis
	Long COVID	Signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)
CDC/WHO	Multisystem inflammatory syndrome in children (MIS-C) or adults (MIS-A)	Symptoms appear between 2 and 6 weeks (4 weeks on average) after COVID-19 infection

Table 2 Summary of clinical manifestations during post-COVID-19 syndrome [12]

Category	Clinical manifestations
Systemic manifestations	Fatigue, poor concentration, restriction of daily activities, chronic malaise, and asthenia
Respiratory manifestations	Dyspnea, persistent cough, exacerbation of asthma, reduced diffusing capacity of lungs for carbon monoxide (DLCO), persistent radiological abnormalities, and pleurisy
Neuropsychiatric manifestations	Sleep abnormalities, chronic headache, olfactory and gustatory impairments, brain fog, defects in memory and concentration, depression, anxiety, post-traumatic stress disorder (PTSD), dizziness, imbalance, vertigo, psychosis and hallucinations, small fiber neuropathy, postural tremor, pain syndromes, and neurodegenerative disorders
Musculo-skeletal manifestations	Myalgia, joint pain, and small joint arthritis
Cardiac manifestations	Atypical chest pain, chest tightness, palpitations, tachycardia, conduction abnormalities and dysrhythmias, orthostatic hypotension, vasovagal syncope, and postural orthostatic tachycardia syndrome
Vascular manifestations	Phlebitis and thrombophlebitis
Gastrointestinal manifestations	Loss of appetite, abdominal pain, nausea, weight loss, altered bowel motility, irritable bowel syndrome, and dysphagia
Endocrine manifestations	Persistent glycemic abnormalities, subacute thyrotoxicosis, Hashimoto's thyroiditis, Grave's disease, and lipid abnormalities
Renal manifestations	Decreased glomerular filtration rate (GFR) and microhematuria
Dermatological manifestations	Skin rash, telogen effluvium, and nail alterations
Miscellaneous manifestations	Hearing loss, tinnitus, red eyes, and sore throat
Abnormalities in lab test results	Elevated neutrophils, elevated D-dimer, anemia, lipid abnormalities, elevated hemoglobin A1C (HbA1C), reduced serum albumin, abnormal liver function tests, thrombocytosis, coagulation abnormalities, and electrolyte abnormalities

that provide information on the pathophysiological mechanisms of long COVID. However, most of them are putative, or the investigations were conducted on small cohorts and is still a matter of research. The subsequent sections attempt to detail some persistent ones found in the current literature and seek to bridge the gaps.

Pathways of SARS-CoV-2 Invasion into the Nervous System

Prior to understanding the pathophysiological mechanisms that can cause neurological damage, it is essential to understand how the virus may enter the nervous system in the first place. In the currently available literature, different neuroinvasive pathways have been proposed. These can be broadly divided into three—(1.) neural pathways (olfactory nerve and gut-brain axis), (2.) hematogenous dissemination (leaky blood–brain barrier (BBB), paracellular, and “Trojan horse” pathways), and (3.) the cerebrospinal fluid (CSF) route, which will be discussed in detail in the subsequent sections (Fig. 1).

Olfactory Nerve

The prevailing neurological symptoms frequently associated with SARS-CoV-2 infection are anosmia (loss of sense of smell) and sometimes parosmia (distorted sense of smell). The loss of smell can occur due to either conductive or sensorineural anosmia [14]. Sensorineural anosmia may occur

because of damage to the sensory neurons within the olfactory bulbs [14].

During a retrospective analysis involving 114 COVID-19 patients, it was observed that 47% of them experienced olfactory loss [15]. In addition, two fatal cases displayed notable leukocyte infiltration and focal mucosal atrophy in the basal layer of the olfactory epithelium lamina propria [15]. These identified symptoms and pathological alterations in the olfactory epithelium contribute to the hypothesis that the virus may infiltrate the brain through the olfactory nerve. The olfactory nerve is the first cranial nerve (CN I) and enables the function of the olfactory system and sense of smell.

The primary components of the olfactory epithelium include olfactory sensory neurons (OSN), supporting cells, basal cells, and Bowman's gland. OSN dendrites extend to the epithelium's free surface, while their axons traverse through the cribriform plate to reach the olfactory bulb (OB) [16]. Intact coronavirus particles and SARS-CoV-2 RNA were found in the olfactory mucosa and neuroanatomical regions of the olfactory bundle projection, hinting towards the potential of olfactory nerve-mediated neuro-invasion by SARS-CoV-2 via axonal transport [16].

Single cell sequencing technology revealed elevated levels of ACE2 and TMPRSS2 expression in support cells, olfactory neural stem cells, and perivascular cells [17]. In addition, ACE2 expression was identified in basal cells and Bowman's gland. Zhang et al. conducted a study revealing that in a hamster model, the infection of the olfactory epithelium extends from the basal cells to both immature and

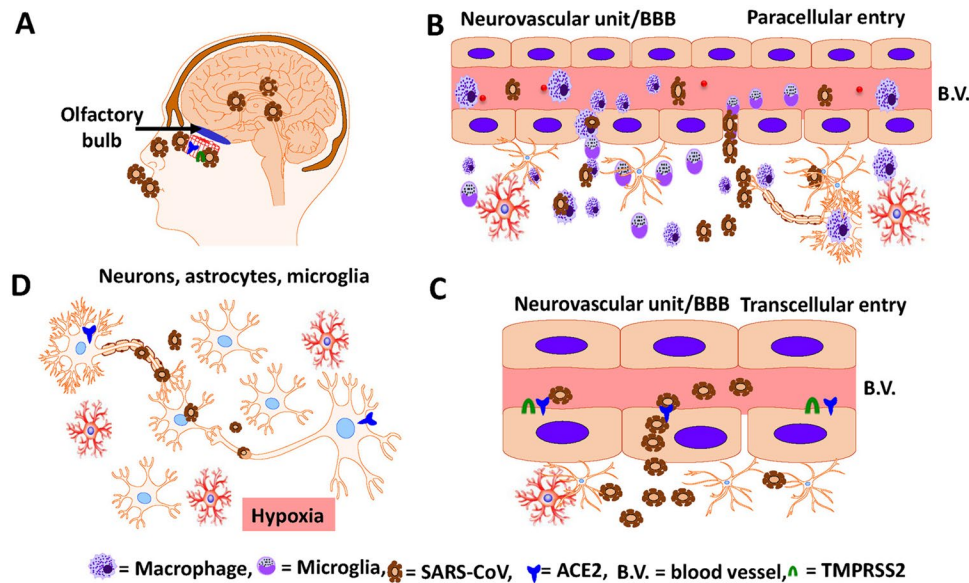


Fig. 1 Various neuroinvasive pathways involved in transmission of SARS-CoV-2 [13]. **A** SARS-CoV-2 can potentially reach the brain parenchyma through the olfactory epithelium and the olfactory bulb (OB). **B** Peripheral monocytes and macrophages infected with SARS-CoV-2 can cross a disrupted blood–brain barrier (BBB) to enter the

brain, where they can infect brain cells. **C** SARS-CoV-2 may directly cross a defective BBB through the damaged or dysregulated/disorganized/deranged tight junction and adherens junction proteins. **D** SARS-CoV-2 can enter the brain through retrograde neuronal transmission (figure adapted from Kempuraj et al. 2023)

mature OSN [18]. This observation implies the possibility of the virus entering the CNS via the olfactory nerve. Bryche et al. noted significant impairment of the olfactory epithelium in hamsters infected through the nasal route, along with a substantial influx of immune cells [19]. This observation provides support for the infection of the olfactory epithelium by SARS-CoV-2.

Apart from the detection of ACE2 expression in the olfactory epithelium, Cantuti-Castelvetri et al. also identified elevated neuropilin-1 (NRP1) expression in OSN, potentially intensifying the susceptibility to SARS-CoV-2 [20]. NRP1 possesses the capability to bind to the conserved C-terminal motif within the S1 subunit of the S protein, thereby promoting TMPRSS2-mediated cell entry of SARS-CoV-2 [20].

While some authors accept the theory that SARS-CoV-2 uses the olfactory nerve as a portal to brain infection, others argue that there are inconsistencies with this theory [21]. The obligatory receptor proteins for virus entry, ACE2 and TMPRSS2, are not expressed in OSN, raising doubts about the entry and travel to the brain through axonal transport. In addition, SARS-CoV-2 rarely infects the olfactory receptor neurons. Instead, researchers have suggested another potential pathway to invade the brain—a cranial nerve that runs close to the olfactory nerve called the nervus terminalis [22]. The nervus terminalis establishes a direct connection between the olfactory epithelium and brain structures located posterior to the olfactory bulb. It was reported that a significant proportion of neurons within the nervus terminalis

express ACE2 [22]. Given that the nervus terminalis directly connects the olfactory epithelium to the hypothalamus, the authors inferred that this could serve as a potential pathway for the virus to access the brain [23]. Currently, the question of SARS-CoV-2 infecting OSN and the OB remains a subject of controversy, underscoring the necessity for additional experimental data to clarify this aspect.

Gut-Brain Axis

Numerous communication channels link the brain and the gut, including the modulation of the immune system, enteric nervous system, neuroendocrine system, circulatory system, and the vagus nerve through the generation of neuroactive substances, hormones, and metabolites (Fig. 2). In recent years, there has been a growing body of research exploring the interplay among the enteric nervous system (ENS), intestinal microecology, and the CNS. The concept of brain-gut peptides has unveiled a closely intertwined connection between the nervous system and the GI tract. The gut-brain axis comprises visceral sensory neurons and autonomic motor neurons that provide innervation to the GI tract. Sensory neurons convey information related to nutrients as well as non-nutrient-related factors (e.g., inflammation, pain) to the brain [24]. Meanwhile, motor neurons play a role in regulating GI motility and secretion [24].

Research on human small intestinal organoids has revealed that intestinal epithelial cells are vulnerable to

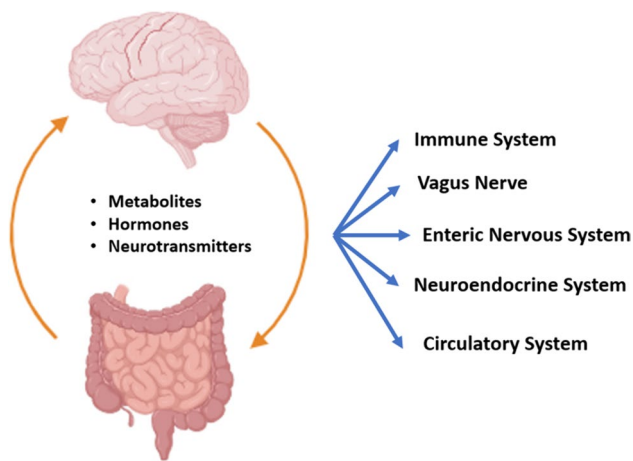


Fig. 2 Bidirectional communication between the gut microbiome and brain. Several pathways of communication exist between the brain and the gut such as the modulation of immune system, enteric nervous system, neuroendocrine system, circulatory system, and the vagus nerve via the production of neuroactive substances, hormones, and metabolites. Infection with SARS-CoV-2 can dysregulate the gut-brain axis (created with Biorender.com)

infection by both SARS-CoV and SARS-CoV-2 [25]. Studies indicate the expression of ACE2 and TMPRSS2 on enteric neurons and intestinal glial cells, with ACE2 being most prominently expressed at the brush border of human intestinal epithelial cells [24]. Upon entering the intestine, SARS-CoV-2 infiltrates the ENS by binding to ACE2 [26]. Given the synaptic connections between neurons in the ENS and the vagus nerve, the virus may proceed to access the brain through the vagus nerve, thereby influencing CNS function [26]. A study further noted a significant reduction in the neurotropic virus load in the brain through intestinal infection following vagotomy in rats [24]. Therefore, these findings indicate that the gut-brain axis could be one of the potential neuroinvasive pathways.

Blood–Brain Barrier

The BBB, consisting of vascular endothelial cells, astrocytes, pericytes, and the basement membrane, serves the crucial role of preserving the stability of the central nervous system's internal environment [27]. ACE2, prominently expressed on vascular endothelial cells, is also found in olfactory epithelial cells, the corpus striatum, cerebral cortex, substantia nigra, and brainstem [28, 29]. In brain microvessels, the expression of CD147/basigin (BSG) and NRP1 is higher compared to ACE2 [30]. BSG, found on the surface of epithelial and immune cells, has been suggested as an alternative potential receptor for SARS-CoV and SARS-CoV-2 infections and could potentially interact with cathepsin L (CTSL) to facilitate cell invasion [28].

A study reported the discovery of SARS-CoV-2 in neurons and capillary endothelial cells within the frontal lobe tissue of a COVID-19 patient during an autopsy [31]. This finding constituted the initial evidence indicating the potential direct transmission and presence of SARS-CoV-2 in human brain tissue. Following entry into the bloodstream, SARS-CoV-2 directly infects vascular endothelial cells owing to the widespread expression of ACE2, TMPRSS2, and NRP1 [28]. Within the cerebral circulatory system, the sluggish flow of blood in microcirculation may enhance the interaction between SARS-CoV-2 spike proteins and ACE2 expressed in the capillary endothelium, potentially facilitating the invasion of the CNS [32].

In another study, Meinhardt et al. observed the presence of S protein in the cytoplasm of the endothelium of small vessels in the CNS of COVID-19 patients using immunostaining [16]. In addition, Varga et al. documented the passage of SARS-CoV-2 through the endothelium into the CNS with the assistance of electron microscopy [33]. Magnetic resonance imaging (MRI) scans of COVID-19 patients revealed enhancement around intracranial lesions and the existence of microhemorrhage foci, implying potential endothelial damage and increased permeability of the BBB [34]. Rhea et al. observed that intravenously injected radioactive iodinated S1 (I-S1) easily traversed the BBB in male mice with the assistance of ACE2 and was absorbed by the corresponding area and entered the brain parenchyma [35]. Furthermore, the presence of SARS-CoV-2 mRNA in the cerebrospinal fluid of mice was detected, providing additional confirmation of its ability to cross the BBB.

An increasing amount of evidence highlights the crucial role of endothelial damage in the pathophysiology of long COVID. One potential explanation is that certain forms of long COVID disproportionately affect individuals with connective tissue disorders, making them more susceptible to significant endothelial and vascular extracellular matrix damage due to the inflammatory processes triggered by COVID-19 [36]. Another hypothesis proposed suggests that a mild initial infection is more likely to cause severe and long-lasting vascular damage in individuals with connective tissue disorders. This hypothesis is supported by a study of 229 individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The study found that half of the participants exhibited generalized joint hypermobility, a marker of connective tissue disorders, based on thresholds linked to the 5th percentile of a large sample stratified by age and gender [36].

Paracellular Pathway

SARS-CoV-2 might enter the CNS by disrupting tight junctions (TJs) between endothelial cells [37]. Tight junctions, also referred to as zonula occludens, act as barriers

preventing substances from crossing the intercellular space. They mainly consist of claudin, occludin, and junctional adhesion molecules (JAMs), with claudin-5 being the most abundantly expressed tight junction protein in the BBB [38]. A study illustrated that elevated levels of beta-secretase 1 in human brain microvascular endothelial cells led to a reduction in the levels of tight junction proteins such as ZO-1, occludin, claudin-1, and claudin-5 [39]. In addition, Rauti et al. conducted experiments with cultured human umbilical vein endothelial cells (HUVECs) and verified that beta-catenin, cadherin-5, and occludin were influenced by SARS-CoV-2 proteins in HUVECs [37].

In contrast, a study by Ashour et al. concluded that, despite the identification of SARS-CoV-2 infection in the brain, TJs were found to be unaffected in virus entry and pathogenesis [38]. This implies that neither claudin-5 nor TJs play a role in the pathogenesis of neuronal injury. In another study, no significant damage to tight junctions was observed in infected K18-ACE2 mice or hamsters [17]. Immunostaining further revealed that the expression and mRNA levels of tight junction-related proteins, such as claudin-5, ZO-1, and occludin, were not significantly reduced [17]. This suggests that the crossing of the BBB by SARS-CoV-2 was accompanied only by the disruption of the basement membrane, without altering TJs. Currently, there is limited research on the entry of SARS-CoV-2 into the CNS through the paracellular pathway, and further exploration is required to elucidate the underlying mechanisms.

The “Trojan Horse” Pathway

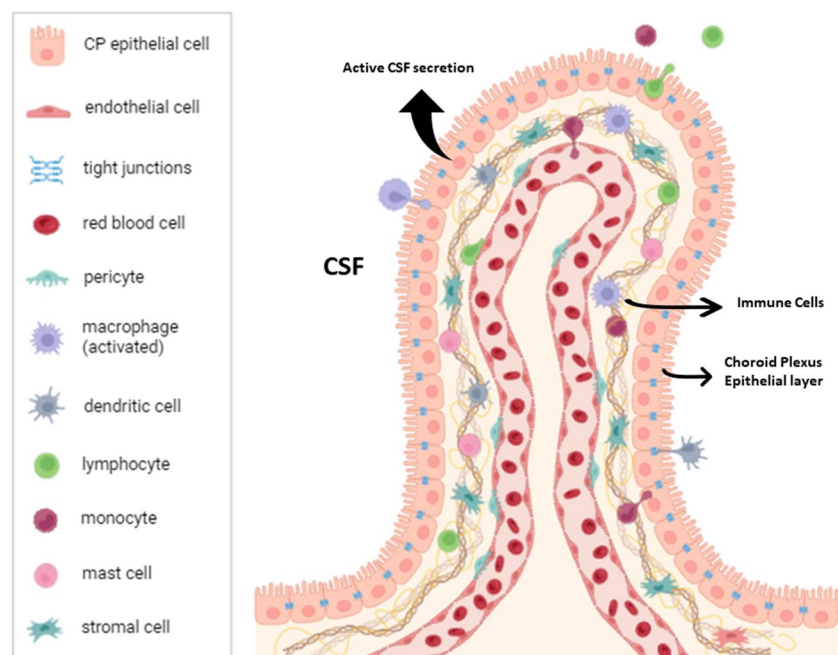
SARS-CoV-2 infection causes activation of a diverse range of immune cells such as monocytes/macrophages, T cells, neutrophils, and natural killer cells (NK cells), and infected immune cells could function as a “Trojan horse” [28]. Research has demonstrated the expression of ACE2 on macrophages in the spleen and lymph nodes and immunohistochemical staining of autopsy-derived specimens revealed the presence of SARS-CoV-2 in macrophages, particularly in resident CD169⁺ macrophages within lymphoid organs. Peripheral lymphocytes, macrophages, and neutrophils, when infected, can potentially act as carriers for the transmission of the virus to the brain [28]. This transmission may occur through various routes, including the vasculature, meninges, or choroid plexus [28].

Cerebrospinal Fluid Route

The blood–CSF barrier, situated at the ventricular choroid plexus and primarily formed by tight junctions among the epithelial cells, separates blood from cerebrospinal fluid (Fig. 3). Research findings indicate that ACE2 and TMPRSS2 are expressed by choroid plexus epithelial cells, predominantly within lysosomes or sizable cytoplasmic vesicles [28, 40, 41]. This suggests that the cerebrospinal fluid could serve as an additional potential route for viral invasion into the central nervous system.

An investigation using a human brain organoid model revealed that SARS-CoV-2 infection resulted in harm to the choroid plexus epithelium, leading to epithelial leakage [40].

Fig. 3 CSF route as a potential pathway for SARS-CoV-2 neuro-invasion. Blood-CSF barrier, made up of choroid plexus epithelial cells, prevents harmful substances from entering the brain and can serve as a route for viral entry as ACE2 and TMPRSS2 are highly expressed in the lysosomes and cytoplasmic vesicles. The blood-CSF barrier can serve as an easily accessible site within the brain due to fenestrated and leaky capillaries (created with BioRender.com)



This was evident through a reduction in the volume of fluid resembling CSF within the infected organoid. In another study, a case of SARS-CoV-2 infection was documented with a positive detection of the virus in the CSF through PCR [42]. The patient presented with fever and syncope, and the virus was exclusively found in the nervous system without affecting other organs [42]. This was interpreted as a straightforward encephalitis caused by SARS-CoV-2, possibly highlighting the virus's ability to directly invade the human brain through the CSF route.

Hypotheses of Underlying Neurological Manifestations

The most common, persistent, and disabling symptoms of long COVID are neurological, which is popularly known as NC-PASC, as previously mentioned (Table 3). Some are easily recognized as brain or nerve-related, and many people experience cognitive dysfunction. Acute and chronic neurological and neuropsychiatric symptoms encompass fatigue, headache, dysautonomia, peripheral neuropathy, anosmia, ageusia, cognitive impairment, depression, and anxiety [43]. Notably, a prevalent long-term neurological consequence is a condition termed COVID-19 brain fog marked by diminished attention, concentration, memory, information processing speed, and executive function.

The pathogenic mechanisms underlying the above-mentioned neurological symptoms of long COVID are not fully understood; nevertheless, various hypotheses suggest

involvement of both nervous system and systemic factors (Fig. 4).

These may include but are not limited to the following: SARS-CoV-2 viral persistence and neuro-invasion, neuro-inflammation, autoimmunity, reactivation of latent herpes-viruses, metabolic dysfunction affecting neural cells, neural glial cell reactivity, BBB disruption, formation of micro clots, chronic tissue hypoxia caused by coagulopathy, and vascular endotheliopathy. It is essential to note that these pathways may or may not be mutually exclusive from each other. Some of these will be discussed in detail in the following sections.

Neuroinflammation

The diverse array of immune cell types, along with variations in chemokine and cytokine production and the presence of inflammatory molecules, has been extensively studied in the context of the immunological response to SARS-CoV-2 infection. This research aims to provide insights into the underlying causes of certain neurological symptoms observed in long COVID. Persistent systemic inflammation has been more thoroughly understood, resulting in the expansion of monocyte subsets and dysregulation of T cells [43]. This, in turn, is linked to dysfunction in the BBB, reactivity in neural glial cells, and demyelination of subcortical white matter [44].

Following infection with SARS-CoV-2, various systemic inflammatory processes become heightened, and certain immune cell populations undergo expansion (Fig. 5). This

Table 3 Manifestations of NC-PASC [28]

Neurological symptoms	Affected regions
Acute cerebrovascular disease	Cerebral vessels
Meningitis/encephalitis	CSF
Acute hemorrhagic necrotizing encephalopathy	Temporal lobe
Posterior reversible encephalopathy syndrome	Cortex
Demyelinating lesion	Spinal cord
Seizure	Left temporoparietal lobe
Ischemic stroke	Cortex
Dizziness	Whole brain
Headache	Whole brain
Ataxia	Whole brain
Impaired consciousness	Whole brain
Brain edema	Brainstem
Anosmia	Olfactory neurons
Ageusia	Tongue nerves
Dysopia	Optic nerves
Guillain-Barré syndrome	Peripheral nerve demyelination
Miller Fisher syndrome	Whole brain
Myalgia	Neuromuscular junction
Rhabdomyolysis	Muscle

Fig. 4 Pathophysiological mechanisms affecting the nervous system. Neurological complications may be attributed to various pathophysiological mechanisms such as neuroinflammation, direct invasion of SARS-CoV-2 into the nervous system, microclots in the cerebral blood vessels leading to hypoxia, and neural glial cell reactivity and reactivation of latent herpesviruses (created with BioRender.com)

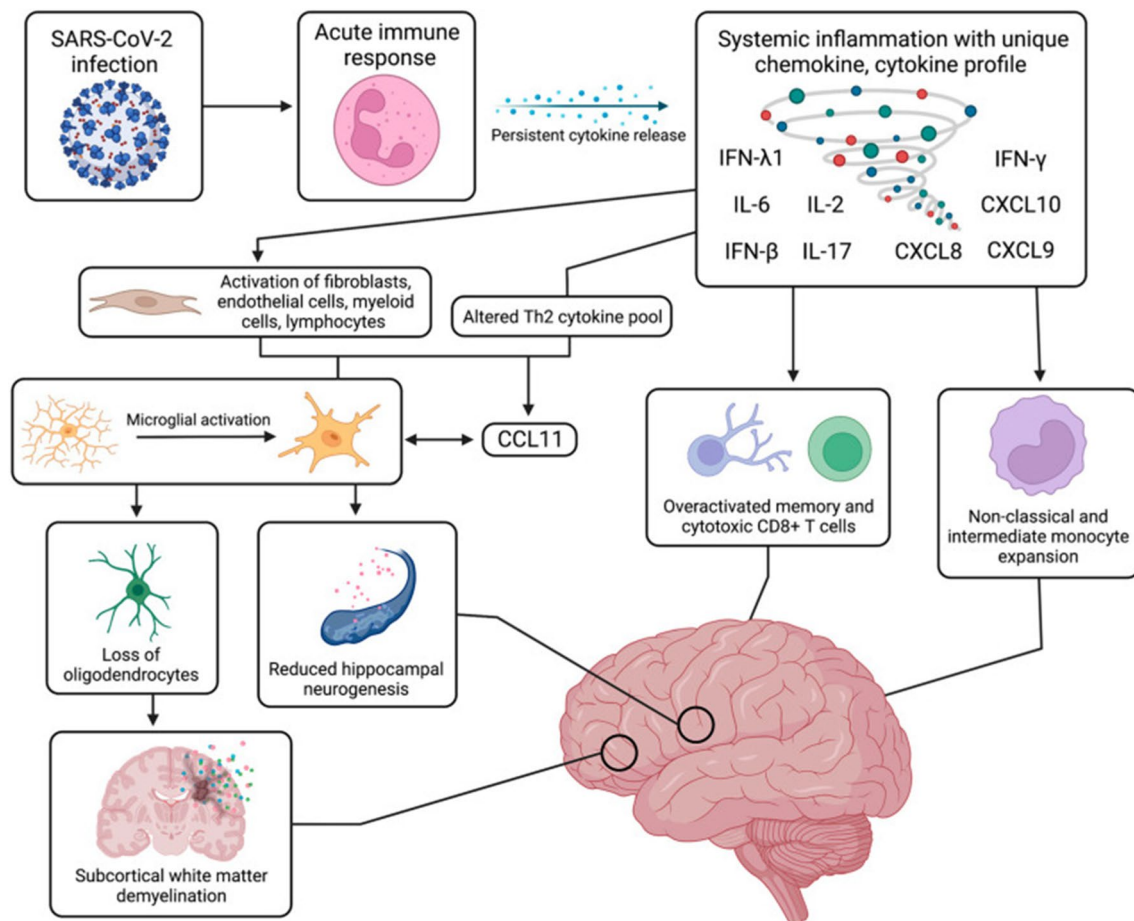
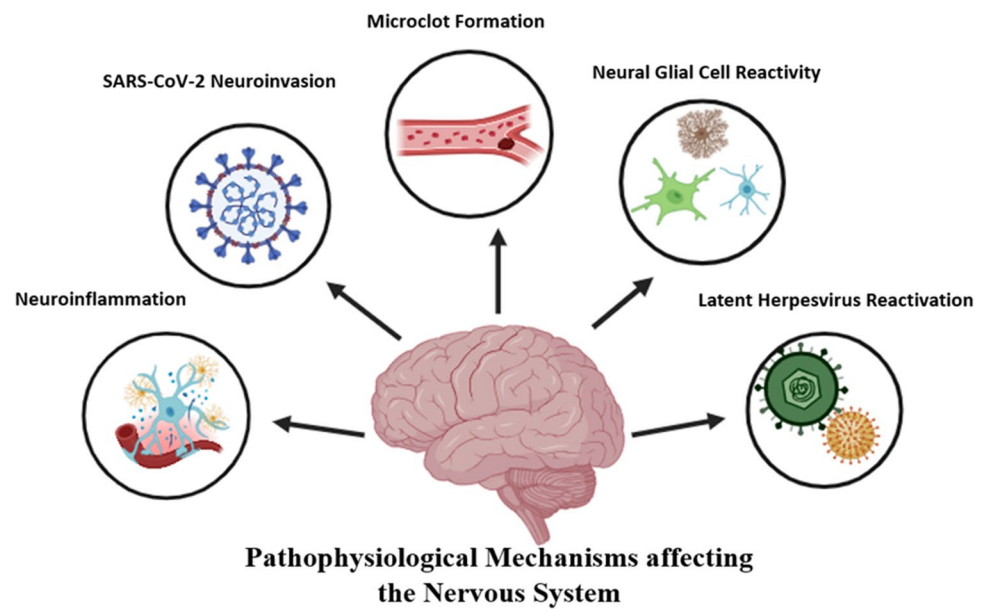


Fig. 5 Neuro-inflammatory manifestations post infection with SARS-CoV-2[43]. Upon acute viral infection with SARS-CoV-2, systemic inflammation may be induced leading to cytokine and chemokine release with a unique profile. This altered profile may, in turn, induce to several changes like activation of fibroblasts, myeloid cells, lymphocytes, endothelial cells, an altered Th2 cytokine pool, overactivation of microglial cells leading to increase in CCL11 expression, and expansion of certain immune cell populations (figure adapted from Leng et al. 2023)

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disruption of the peripheral immune system may endure for several months post-infection, potentially resulting in neurological symptoms. In a general sense, individuals who had recovered from COVID-19 displayed variations in the populations of innate immune cells, including NK cells, mast cells, and macrophages with CXCR3⁺, as well as adaptive immune cells like T-helper cells and regulatory T cells, when compared to healthy controls [45]. With non-naïve phenotypes, these cells typically release and respond to elevated levels of cytokines and inflammatory markers. This includes, but is not restricted to, IFN- β , IFN- λ 1, CXCL8, CXCL9, CXCL10, IL-2, IL-6, and IL-17 [46, 47].

Numerous studies have highlighted a notable resemblance between the symptomatology of long COVID and mast cell activation syndrome (MCAS). In MCAS, abnormal mast cell activation triggers an excessive release of inflammatory mediators, including type 1 interferons (IFNs), and activates microglia through cytokine activation [48, 49]. Activated by viral entry, these mast cells are frequently located at interfaces between tissues and the environment. They might play a role in sustaining systemic inflammation and microvascular dysfunction, leading to CNS disturbances in long COVID [48, 49].

Moreover, a study employing flow cytometry to analyze the peripheral blood of long COVID patients observed an increased expansion of non-classical monocytes (CD14^{dim}CD16⁺) and intermediate monocytes (CD14⁺CD16⁺), persisting for up to 15 months post-infection, in comparison to healthy controls [50]. From a physiological perspective, non-classical monocytes play a role in complement-mediated and antibody-dependent cellular phagocytosis in response to viral threats. They are frequently located along the luminal side of vascular endothelium, contributing to the integrity of the BBB. Notably, severe long COVID patients were observed to have heightened levels of macrophage scavenger receptor 1 (MSR1), indicating a significant degree of peripheral macrophage activation. This activation, in turn, has the potential to disrupt the BBB and induce tissue damage [51].

While this pronounced systemic hyperinflammatory state has not been proven to directly induce neuropsychiatric manifestations, it might contribute to the progression of the disease through the chronic activation of specific T cell and monocyte populations and neurovascular dysfunction of the BBB. These mechanisms could lead to the migration of inflammatory molecules and immune cells from the periphery into the CNS, instigating a persistent neuroinflammatory response.

Autoimmunity

An additional mechanism through which COVID-19 may harm the nervous system is by triggering autoimmunity.

Rather than being a direct result of the virus, the autoimmune antibody reaction is proposed to be a consequence of the notable immune and inflammatory response [52, 53]. Serologically detected autoantibodies can be classified based on their targets into antibodies against extracellular, cell surface, and membrane components, or intracellular targets. This includes immunoglobulin G (IgG) and immunoglobulin A (IgA), anti-ACE2, and ANA antibodies, respectively [43]. After the activation of B cells in the periphery and the occurrence of cytokine abnormalities, these serologic IgG and IgA antibodies display a polyclonal distribution. They impact cytokine function and endothelial integrity, with the potential to enter the CNS due to the disruption of the BBB [43].

In a study involving six individuals hospitalized for COVID-19 with acute neurological symptoms, single-cell transcriptomic analyses of immune cells in both blood and CSF uncovered activated T cells [54]. In addition, there was clonal expansion of distinct T cell clones in the CSF that were not present in the blood, indicating a compartmentalized T cell response to a CNS antigen. An increase in B cells in the CSF when compared to controls was also observed. This enrichment included specific CSF plasma cell clusters, resulting in correspondingly distinct anti-SARS-CoV-2 antibodies found in both the CNS and peripheral compartments [54]. Upon analyzing the antibodies isolated from a patient's CSF, it was discovered that there were antibodies reactive with neural antigens, including those associated with neurons [54]. In a separate study encompassing 172 hospitalized patients with moderate and severe COVID-19, a varied array of serum autoantibodies was identified [55]. These autoantibodies targeted vascular cells, coagulation factors, platelets, connective tissue, extracellular matrix components, and various organ systems, encompassing the CNS.

Autoimmunity is also a cause for autonomic dysfunction, which is one of the debilitating effects of long COVID that causes patients to experience fatigue, dizziness, syncope, dyspnea, POTS, nausea, vomiting, and heart palpitations [56]. Receptor autoantibodies have the capability to influence cell function and initiate alterations in the synaptic connections between neurons [56]. Patients suffering from long COVID with neurological symptoms exhibit variable levels of autoantibodies against adrenergic A1 receptors, adrenergic B2 receptors, muscarinic M2 receptors, nociceptin receptors, endothelin receptors, MAS receptors, and angiotensin II AT1 receptor, but only the autoantibodies against adrenergic B2 and muscarinic M2 receptors are present in all recovered patients [53].

In a recent cross-sectional study that included 200 patients, it was shown that autoantibodies targeting G-protein coupled receptors (GPCR) were commonly present in individuals experiencing long COVID [57]. Out of these, 66.2% exhibited at least one of the examined autoantibodies

(antibodies against adrenergic receptor, muscarinic acetylcholine receptor, angiotensin II receptor type 2, and endothelin receptor type A) [57]. While these autoantibodies were also present in healthy controls, their occurrence was significantly lower, at 16% [57]. Patients who recovered from COVID-19 without lingering symptoms showed a higher prevalence of autoantibodies compared to healthy controls, but a lower prevalence compared to patients experiencing long COVID. In addition, the presence of autoantibodies was directly linked to the severity of both cognitive and physical impairment. The study revealed that elevated levels of multiple autoantibodies were associated with an unfavorable outcome in an assessment tool testing psychomotor coordination, visuospatial skills, visual processing speed, and executive function. This implied a potential role of GPCR in the diminished mental state related to long COVID. However, the study's design does not allow for the investigation of causality in the observed association [57]. Hence, one can only speculate about the potential role of the identified autoantibodies in the development of long COVID. Additional studies incorporating a larger number of patients, sequential sampling, and exploratory marker analyses are necessary to provide further insights.

Reactivation of Latent Herpesviruses

Healthy adults carry various viruses, especially those belonging to the Herpesviridae family, in a dormant state. These dormant viruses generally remain asymptomatic. However, an acute viral infection can prompt the reawakening of these latent viruses, leading to the generation of infectious viral particles that may induce notable inflammation and symptoms. In addition to the persistence of the SARS-CoV-2 virus, long COVID patients have also been documented to experience the reactivation of herpesviridae family viruses, such as Epstein-Barr virus (EBV) and Varicella-Zoster virus (VZV) [43]. After the initial infection, both viruses can remain dormant in host cells, with EBV residing in memory B cells and VZV in the neurons of sensory ganglia [43]. Under the influence of stressors, such as another acute viral infection, these latent herpesviruses can reactivate, triggering inflammation and neurological symptoms. In the context of COVID-19 and long COVID, SARS-CoV-2 may serve as a stressor capable of precipitating the reactivation of other viruses and contributing to the symptomatic manifestation.

In an early retrospective study of individuals recovering from acute COVID-19 and post-hospitalization, it was observed that 25% of patients with severe disease exhibited elevated serological titers of EBV early antigen IgG (EA-IgG) and viral capsid antigen IgG (VCA-IgG) [58]. These increased titers are indicative of virus reactivation for which EA-IgG and VCA-IgG serve as proxy markers [58].

In the context of long COVID, a survey study revealed that approximately two-thirds of patients experiencing symptoms 90 days after their initial SARS-CoV-2 infection tested positive for EBV reactivation as demonstrated by positive titers of VCA-IgG and EA-D IgG [59]. Patients experiencing a higher frequency of long COVID symptoms showed a significant correlation with elevated titers of EA-IgG. In addition, a longitudinal study involving 309 patients, tracked from primary infection to convalescence, identified EBV viremia as one of the four primary risk factors associated with the development of long COVID symptoms [59]. The other three risk factors were type II diabetes, SARS-CoV-2 RNAemia, and the formation of autoantibodies [60].

Beyond COVID-19, the immune response triggered by EBV reactivation has demonstrated similarities to that observed in ME/CFS [61]. This connection suggests that EBV viremia may be linked to the development of ME/CFS-like symptoms in individuals experiencing long COVID. In a cross-sectional study involving 215 long COVID patients, an immune profile was identified, showcasing heightened antibody reactivity to EBV gp23, gp42, and EA-D. These elevated antibody levels were found to correlate with IL-4 and IL-6 producing CD4⁺ T cells [62]. In the same study, notable levels of antibody reactivity to the VZV glycoprotein E were also identified. This reactivity was similarly linked to the immune profile previously mentioned, indicating a correlation with IL-4 and IL-6 producing CD4⁺ T cells [62]. While VZV reactivation may play a less prominent role in the pathogenesis of long COVID compared to EBV reactivation, it can still contribute to neurological symptoms. This is attributed to VZV's involvement with the CNS.

Metabolic Alterations

Research on putative biomarkers of long COVID have shed light on the metabolic and immune alterations in long COVID patients when compared to healthy individuals or recovered individuals without long COVID syndrome. In a systemic review published in 2023, biomarkers of long COVID and their roles in disease progression were evaluated [63]. From a compilation of 28 studies spanning six biological classifications, a total of 113 biomarkers were found to be significantly associated with long COVID. Of note, one of the important classifications, neurological biomarkers, has been listed (Table 4).

Regarding biochemical markers linked with metabolism, individuals with COVID-19 who exhibited heightened levels of LDH tended to manifest long COVID symptoms. Moreover, concerning neurological and vascular markers, patients with increased levels of neurofilament light chain (NFL) and vascular endothelial growth factor (VEGF), coupled with decreased hemoglobin, experienced more severe long COVID symptoms.

Table 4 Classification of neurological biomarkers significantly associated with NC-PASC

Category	Biomarkers
Acute phase protein	Albumin, CRP, ferritin, fibrinogen
Biochemical marker	β -glucan, and S-sulfocysteine
Cytokine/chemokine	CCL2, IFN- γ , IL-4, IL-6, and TNF- α
Neurological marker	GFAP, NFL, and pGFAP/pNFL
Vascular marker	ET-1, hemoglobin, sICAM-1, sVCAM-1, and sVEGFR
Others	Ab, Hs TnT, and IGFBP-4

When metabolic changes in patients with long COVID were assessed in a recent study, 50% of the analyzed plasma metabolites exhibited statistically significant differences between the COVID-19 phase and the long COVID phase [64]. Taurine was notably reduced during the long COVID phase, and the diminished levels observed could potentially contribute, at least in part, to the fatigue experienced by patients as taurine plays various roles in skeletal muscle function, central nervous system regulation, and energy metabolism [64]. It was also revealed that long COVID patients exhibited elevated levels of metabolites linked to collagen metabolism [64]. Notably, among these metabolites, proline stands out due to its crucial role in protein structure and function, as well as its involvement in maintaining cellular redox homeostasis through the generation of adenosine triphosphate (ATP) and reactive oxygen species (ROS) during its breakdown [64]. Of note, this study was the first to detail quantitative metabolic perturbations 2 years after the initial acute COVID-19 infection through targeted metabolomics. Accordingly, the progression of long COVID in patients appears to be unique, with symptoms linked to distinct metabolic patterns that, to some degree, resemble those observed in the ME/CSF condition.

Some patients with long COVID exhibit symptoms like those of ME/CFS, leading to a significant reduction in their quality of life. In a study published in 2024, metabolites and soluble biomarker in plasma were identified and studied from 30 long COVID individuals (LC) mainly exhibiting ME/CFS compared to 15 age-sex-matched recovered individuals (R) without LC, 15 acute COVID-19 patients (A), and to 15 SARS-CoV-2 unexposed healthy controls (HC) [65]. A total of 2584 metabolites were detected from 75 plasma samples. Partial least squares-discriminant analysis (PLS-DA) and the heatmap revealed a distinct classification of metabolomes across the four groups (Fig. 6).

While the LC and HC groups were distinct, the R group was intermediate. At the single metabolite level, volcano plots showed 478 metabolites significantly reduced and 294 increased in acute (A) COVID-19 patients compared to HCs. In the R group, 103 metabolites were elevated and

123 decreased compared to HCs. Between LC and HC groups, 61 metabolites were decreased and 76 increased. Acute patients and the R group had 419 increased and 285 decreased metabolites. Compared to acute patients, LC patients had 495 metabolites reduced and 167 elevated. LC patients showed 49 reduced and 111 increased metabolites compared to the R group. The top 100 altered metabolites revealed that acute COVID-19 patients had a distinct profile from HCs and the R group. Though R individuals were generally distinct from HCs, three R patients were like HCs. LC patients were distinct from both the R and HC groups based on the top 100 metabolites. These findings indicate that both LC and R individuals have altered metabolomic profiles even 12 months post-acute disease onset.

In a separate study involving 21 NC-PASC patients, 45 healthy volunteers, and 26 patients with inflammatory neurological diseases, researchers aimed to elucidate and uncover the SARS-CoV-2-associated molecular pathophysiological changes in CSF [66]. Metabolomic and proteomic analyses of CSF revealed notable differences between NC-PASC patients and healthy volunteers. Elevated levels of sphinganine and ST1A1, along with disrupted sphingolipid metabolism and a weakened inflammatory response, imply potential mechanisms contributing to NC-PASC [66]. The reduced levels of 7,8-dihydropterin and the increased activity of steroid hormone biosynthesis pathways could indicate a reparative mechanism in NC-PASC [66]. In addition, this study demonstrated that biomarker panels comprising 7,8-dihydropterin, sphinganine, and ST1A1 accurately distinguished NC-PASC patients from healthy volunteers. This study marks the first attempt to elucidate the metabolomic and proteomic characteristics of CSF in NC-PASC patients and successfully identified a biomarker panel for diagnosing NC-PASC. However, this study was conducted on a small cohort. Therefore, it is imperative to expand the cohort size to better delineate the precise neurological changes induced by SARS-CoV-2 and to evaluate the effectiveness of biomarkers in diagnosing NC-PASC.

Formation of Microclots

During the acute phase of infection, COVID-19 is recognized for its tendency to heighten the likelihood of hemorrhages, ischemic infarcts, and hypoxic alterations in the central nervous system, suggesting that coagulopathy plays crucial roles in the mechanisms of pathogenesis [67]. Although these neurological symptoms are not observed in high frequency among long COVID patients, small vessel thromboses (microclots) and microvascular dysfunction due to persisting mechanisms of coagulopathy could account for the neurological symptoms of long COVID that are associated with cerebrovascular disease and hypoxic-neuronal injury (Fig. 7) [68].

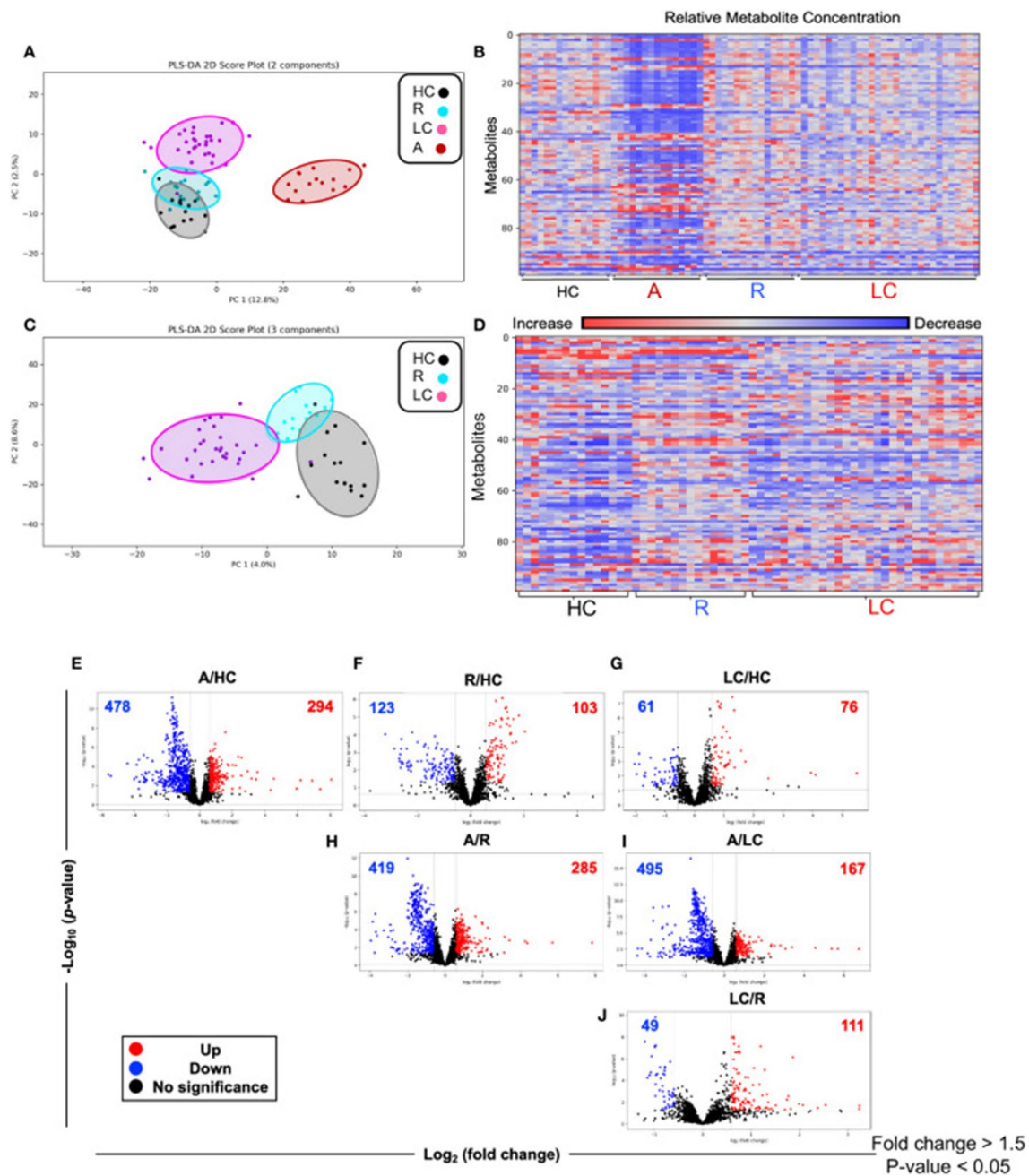


Fig. 6 Altered metabolomic profiles of long COVID patients (LC), recovered individuals (R), healthy controls (HC), and patients with severe infection (A)[65]. **A** Partial least squares-discriminant analysis (PLS-DA) plot based on the metabolites in LC ($n=30$), acute COVID-19 ($n=15$), HC ($n=15$), and R ($n=15$). **B** Heatmap based on ANOVA using the top 100 significantly altered metabolites for HC, A, R, and LC, displaying the auto-scaled levels of each metabolite in each sample, with blue indicating decline and red indicating elevation, as shown on the horizontal bar. **C** PLS-DA plot based on the metabolites in LC ($n=30$), HC ($n=15$), and R ($n=15$). **D** Heatmap based on ANOVA using the top 100 significantly altered metabolites for HC, R, and LC, displaying the auto-scaled levels of each

metabolite in each sample, with blue indicating decline and red indicating elevation, as shown on the horizontal bar. **E** Volcano plots of significantly increased (red), decreased (blue), or unchanged (black) metabolites in A vs HCs. **F** Volcano plots of significantly increased, decreased, or unchanged metabolites in acute R vs HCs. **G** Volcano plots of significantly increased, decreased, or unchanged metabolites in acute LC vs HCs. **H** Volcano plots of significantly increased, decreased, or unchanged metabolites in acute A vs R. **I** Volcano plots of significantly increased, decreased, or unchanged metabolites in acute A vs LC. **J** Volcano plots of significantly increased, decreased, or unchanged metabolites in acute LC vs R (figure adapted from Saito et al. 2024)

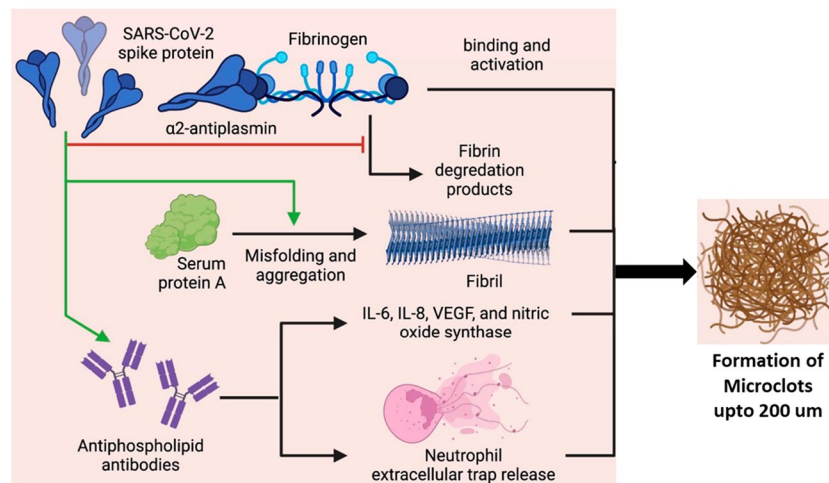


Fig. 7 Mechanism of small vessel thromboses and microvascular dysfunction in long COVID[43]. The spike protein interactions of SARS-CoV-2 with fibrinogen and serum protein A can lead to heightened microclot formation, facilitating fibril formation and impeding fibrinolysis. Antiphospholipid antibodies found in long COVID can instigate microclot formation by triggering the release of IL-6, IL-8,

VEGF, nitric oxide synthase, and neutrophil extracellular trap release. In addition, these microclots encompass α2AP, which inhibits plasmin and consequently hinders the degradation of fibrin, thereby reinforcing their resistance to fibrinolysis (figure adapted from Leng et al. 2023, modified with Biorender.com)

In long COVID, a significant mechanism contributing to thrombosis is characterized by the formation of large anomalous amyloid microclots with a unique signature of fibrinolysis resistance, detected in the serum of affected patients [69]. Thioflavin T staining and microscopy have been employed to ascertain that the size of these microclots can exceed 200 μm and this substantial size has the potential to effectively block microcapillaries, leading to a reduction in cerebral blood flow and consequent ischemic neuronal injury [69, 70]. The formation of microclots arises from the interaction between the SARS-CoV-2 spike protein and fibrinogen [70–72]. This binding results in heightened clot density, an enhanced release of reactive oxygen species due to the spike protein, inflammation induced by fibrin at sites of vascular damage, and delayed fibrinolysis. Moreover, the interaction between the nine-residue segment SK9, situated on the SARS-CoV-2 envelope protein, and serum amyloid A (SAA) has been identified as a factor that enhances fibril formation and stability [73]. This interaction plays a role in fostering the amyloid nature of the microclots.

In a proteomic pairwise analysis of digested microclot samples obtained from long COVID patients, there were notable increases in the levels of fibrinogen alpha chains and SAA [69]. Both components contribute to fibrinolysis resistance, ultimately leading to the prolonged persistence of microclots. Furthermore, the same study uncovered a significant elevation of the inflammatory molecule α2-antiplasmin (α2AP), a potent inhibitor of plasmin, in microclots from long COVID patients compared to those with acute COVID [69]. This elevation likely plays a role

in fostering an aberrant fibrinolytic system alongside the formation of anomalous microclots.

Neural Glial Cell Reactivity

The activation of the neuroimmune system, particularly through the interplay of neural and glial cells such as astrocytes, microglia, and oligodendrocytes, is considered one of the primary hypothesized mechanisms behind long COVID symptomatology. Astrocytes, crucial for CNS homeostasis, contribute significantly to neuron–glial cell interaction, synaptic function, and the integrity of the blood–brain barrier. Microglia play a fundamental role in innate immunity processes within the CNS, and they are essential for synaptic function, the maintenance of neural networks, and supporting homeostatic repair mechanisms in response to micro-environmental injuries. However, when there are changes in cytokine activity and instances of brain injury, glial cells have the potential to become overactivated (Fig. 8).

Long COVID patients exhibit elevated levels of ezrin (EZR), leading to the upregulation of NF-κB by reactive astrocytes [51]. This upregulation can trigger endothelial cell death and an increase in extracellular glutamate, ultimately causing disruption to the BBB and hyperexcitability-induced neurodegeneration [74]. Likewise, there is a suspicion that reactive microglia, in the process of losing their ability to promote plasticity, contribute to the disruption of neural circuitry through the release of microglial cytokines [ref]. Long COVID patients experiencing neurological symptoms were discovered to have heightened levels of CCL11 [74, 75]. This immunoregulatory

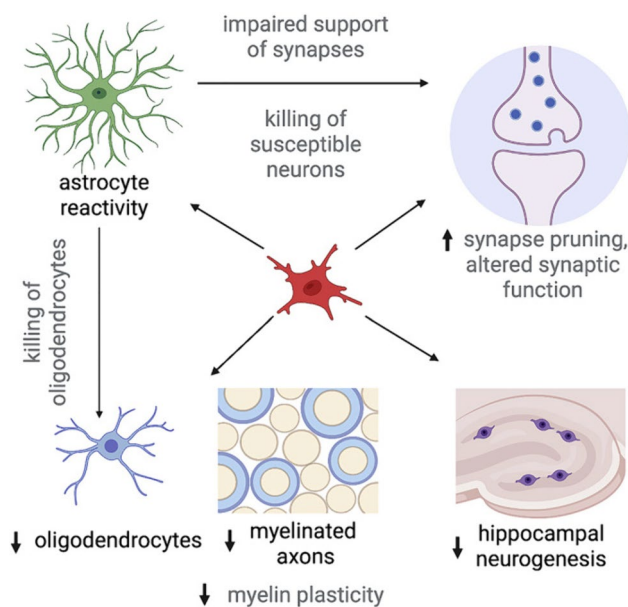


Fig. 8 Mechanism of overactivation of the neuroimmune system in NC-PASC [68]. Reactive microglia can induce complex cellular dysregulation such as reduction in oligodendrocytes and myelinated axons, disrupting myelin homeostasis; reactive astrocytes in a neurotoxic substance can in turn kill oligodendrocytes and susceptible neurons, impairing synaptic functions. Functional microglia also prune synapses and regulate neuronal excitability that gets aberrantly altered when they are overactive. Reactive microglia-derived cytokines like IL-6 and chemokines like CCL11 can impair hippocampal neurogenesis (figure adapted from Monje et al. 2022)

chemokine can recruit eosinophils, cross the blood–brain barrier, induce microglial migration, disrupt hippocampal neurogenesis, and lead to cognitive dysfunction, such as the commonly reported symptom of brain fog [75]. The reduced branching of microglia, in part triggered by CCL11, leads to the release of microglial cytokines and the demise of susceptible neuroglial cells affected such as myelinating oligodendrocytes, crucial for tuning neural circuitry and providing metabolic support to axons [75].

In both mouse models and brain tissue samples from individuals with long COVID, there is notable reactive behavior in microglia and astrocytes, particularly in white matter regions [75]. This reactivity is associated with the subsequent loss of oligodendrocytes and demyelination in subcortical white matter [75]. Consequently, the compromise of circuit integrity may contribute to the persistence of neurological symptoms. In addition, innovative brain organoid models have shown significant microgliosis 72 h after infection, accompanied by the upregulation of IFN-stimulated genes and microglial phagocytosis [76]. This phagocytosis results in the engulfment of nerve termini and the elimination of synapses [76]. The observed destruction of postsynaptic structures may persist, accompanied by persistent chronic microglial reactivity,

potentially contributing to a continued propagation of neurodegeneration in long COVID.

The development of long COVID and neurological symptoms associated with it suggest disruptions in neuroglial cells, leading to reactive changes in glial cells that may be focused on brain areas, such as the olfactory bulb, brainstem, and basal ganglia [74]. In the presence of enduring cytokine irregularities and brain injury, reactive neuroglia can impact vascular and endothelial function, jeopardizing the integrity of BBB [43]. This influence can contribute to neurodegeneration, characterized by significant rises in extracellular glutamate, leading to a state of toxic hyperexcitability [43]. In response to elevated levels of CCL11, reactive microglia release cytokines that can harm neural circuitry [43]. This hyperactive state of microgliosis may result in a reduction in hippocampal neurogenesis, associated with impairments in memory and cognitive function [43]. In addition, it may lead to the death of myelinating oligodendrocytes, thereby contributing to white-matter selective demyelination [43]. To sum up, the predominant neuropathological finding consistently observed in all autopsy-based studies of COVID-19 patients is the notable over-reactivity of astroglial and microglial cells.

Discussion and Future Scope

COVID-19 in the acute phase may be established as a respiratory disease, but its long-term effects can manifest as a multi-organ dysfunction syndrome known as long COVID. After almost 4 years since it was declared as a pandemic, it continues to have a profound impact on public health, disease burden, social and economic status, and quality of life. Although long COVID may not be fully understood in terms of its pathophysiology and, more prominently, the neurological complications and manifestations associated with it, scientists are trying to decipher long COVID with grit and urgency. In this review, proposed neuroinvasive pathways and pathophysiological mechanisms were discussed, particularly those that were found to be persistent in the literature. Growing evidence suggests that the most common and disabling symptoms of long COVID may be neurological. These neurological manifestations may arise in the form of fatigue, brain fog, headache, cognitive impairment, neuropathy, sensorimotor deficits, and dysautonomia. The more serious complications include ischemic and hemorrhagic strokes, encephalopathy, and seizures. Various mechanisms have come into light regarding the neurological damage caused by SARS-CoV-2. Different neuroinvasive pathways have been proposed that help the virus enter the CNS such as through the olfactory nerve, disruption of BBB, and CSF route to name a few. The neurological complications may be attributed to various proposed mechanisms such as

neuroinflammation, autoimmunity, reactivation of latent herpesviruses, neural glial cell reactivity, direct SARS-CoV-2 viral invasion, and formation of microclots, especially in the cerebrovascular regions.

Current evidence suggests that COVID-19 may harm neurons, which could lead to parkinsonian symptoms, and further develop into chronic neurodegenerative disorders. Infectious disease is now recognized as a cause of neurodegeneration, though measuring neurological damage from viral infections remains challenging [77]. The mechanisms behind the delayed onset of neurodegeneration are not well understood, but some evidence points to the prolonged presence of senescent cells, viral particles, and amyloidogenic proteins even after the production of infective virions has decreased or ceased. The Bradford-Hill criteria offers a framework for establishing causality. A direct correlation has been reported between previous SARS-CoV-2 infection and an increased risk of Alzheimer's disease [77]. Given this evidence, SARS-CoV-2 infection may be considered a risk factor for Alzheimer's disease, despite the unclear distinction between causation and disease acceleration [77].

Important questions remain unclear and is a matter of undergoing investigation. Only a fraction of those with severe COVID-19 infection go on to develop long COVID. Those with mild infection nevertheless develop long COVID. Some people may recover from long COVID while others may not. Recovery varies substantially from person to person. What are the factors that sets apart one group from another? The answer may be more complex than the simplicity of the question. Individual variability, viral load and immune response, predisposition to illness, age and demographics, vaccination status, and post-infection rehabilitation may all be equally important contributing factors and may require overlapping or completely different approaches to unravelling their nuances.

Conclusion

In summary, scientists face a challenge in understanding and addressing the root cause of long COVID. Despite the extensive and accelerated research on long COVID, the current body of knowledge falls short in enhancing outcomes for individuals grappling with the condition. Effectively combating the long COVID crisis should include conducting research that builds upon the existing knowledge in the public domain while incorporating the individual needs of the patients. In addition, extensive training and education for doctors, healthcare providers, and researchers should be arranged. Robust policies that underscore a highly international collaborative approach should be given more importance, along with the appropriate funding for research and care for long COVID patients. Likely, the complexity of long

COVID suggests that it may not be attributed to a singular and straightforward mechanism but rather involve multiple root causes influenced by various factors. This underscores the importance of international collaborations among medical societies, the swift and transparent sharing of research data, and an urgent need for fundamental research to delve deeper into the pathophysiological aspects of long COVID. In addition, as society increasingly calls for evidence-based interventions for long COVID patients, it is crucial for scientists to come together in developing preventive and therapeutic strategies. The ultimate objective is to mitigate the widespread impact of an impending long COVID pandemic on communities across the globe.

For the near future, there is a pressing need to establish operational case definitions for long COVID. Secondly, comprehensive documentation of clinical symptoms, signs, risk factors, previous COVID-19 complications, and comorbidities is essential for a systematic approach to managing long COVID patients. Thirdly, multidisciplinary collaboration is vital to deliver comprehensive and integrated care for long COVID patients. Fourthly, early neurorehabilitation, which is characterized by consequences rather than causes, is advisable for individuals experiencing prolonged neurological symptoms after recovering from acute COVID-19. It may include supervised exercise, hyperbaric oxygen therapy, breathing strategies, mindfulness-based practices, and psychological therapies, which may require a team of medical advisors like neurologists, immunologists, physiotherapists, and dieticians. Ultimately, meaningful engagement of these communities within and outside is essential in advancing long COVID research and clinical trials. The insights and experiences of individuals grappling with the illness play a pivotal role in shaping study design, identifying key research questions, and formulating solutions. Such engagement not only accelerates the pace of research but also ensures its alignment with the needs and realities of those directly impacted by the condition.

Author Contribution A.S. wrote the manuscript, prepared the figures and J.M. reviewed the manuscript for editing.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Research Involving Human Participants and/or Animals All the authors listed hereby confirmed that in the above research, there were no human participants and/or animals involved in any kind of determination, evaluation, or research studies. We confirm that the above-mentioned manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other peer-reviewed media.

Conflict of Interest The authors declare no competing interests.

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