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Review Article

Mechanisms of long COVID: An updated review

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has been ongoing for more than 3 years, with an enormous impact on global health and economies. In some patients, symptoms and signs may remain after recovery from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which cannot be explained by an alternate diagnosis; this condition has been defined as long COVID. Long COVID may exist in patients with both mild and severe disease and is prevalent after infection with different SARS-CoV-2 variants. The most common symptoms include fatigue, dyspnea, and other symptoms involving multiple organs. Vaccination results in lower rates of long COVID. To date, the mechanisms of long COVID remain unclear. In this narrative review, we summarized the clinical presentations and current evidence regarding the pathogenesis of long COVID.

Introduction

Long COVID, also known as post coronavirus disease 2019 (COVID-19) syndrome or post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC), is defined as signs and symptoms that develop during or after an infection consistent with COVID-19, which continue for more than 12 weeks, and are not explained by an alternate diagnosis.[1–3]

Long COVID is highly heterogeneous in its clinical presentation. More than 200 different symptoms are ascribed to long COVID.[4] The most commonly reported complaints include shortness of breath, fatigue, brain fog, anosmia, hair loss, sexual dysfunction, and sleep alteration.[5–11] The duration of long COVID symptoms is unclear. We and other researchers have found that patients infected with the original SARS-CoV-2 strain still had long COVID symptoms more than 2 years after hospital discharge.[11–13] The proportion of each symptom changes over time based on a 2-year follow-up study in China, which is summarized in Fig. 1.

Underlying reasons for developing lingering symptoms of COVID-19 infection are unclear. In multiple cohort studies, female sex,[14,15] obesity,[16] and severe COVID-19 disease were identified as the main risk factors. However, long COVID is not limited to only patients with severe forms of COVID-19. Outpatients with mild symptoms during the acute phase may also experience long COVID.[17–19] Interestingly, infection with different SARS-CoV-2 variants is associated with varying long COVID phenotypes,[20] possibly owing to differences in viral–host interactions. Among patients infected with the original virus strain, a higher percentage of them had long COVID than did patients infected with alpha or delta SARS-CoV-2 variants.[21] The omicron variant is associated with a lower risk of long COVID in comparison with the delta variant.[22–25]

The clinical findings and characteristics of long COVID differ among age groups. Older adults are more likely to be symptomatic, with the most common symptoms being fatigue and dyspnea. This group is more likely to have cough and arthralgia, as well as abnormal chest imaging findings and pulmonary function tests.[26] The conditions of children and adolescents are different and more complex in comparison with adults. Several large national studies from Germany, the United Kingdom (UK),[27] Norway,[28] Denmark,[18,29,30] and the United States (US)[31] have contributed further evidence on the health and social impacts of long COVID among children and adolescents, with conflicting results.[18,32] In some studies, no difference was found in long-lasting symptoms between children post COVID and healthy children. More gastrointestinal symptoms of long COVID were observed in immunocompromised children, but fatigue levels were higher in immunocompetent children.[33]

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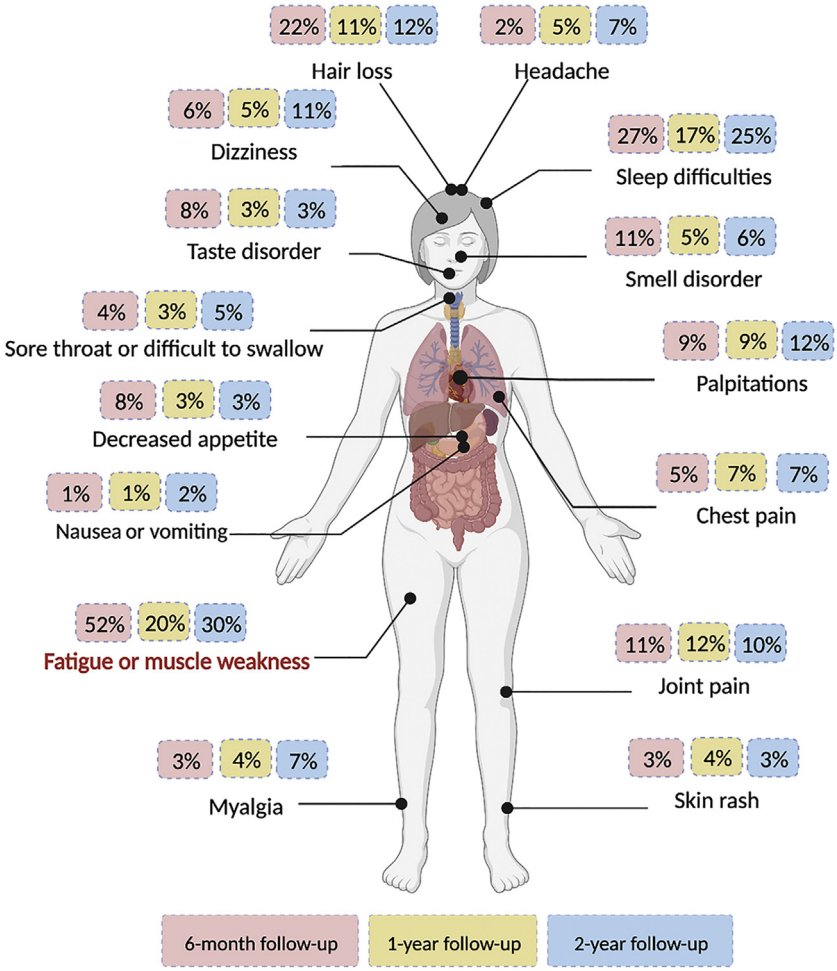

Fig. 1. Symptoms and symptom proportions in long COVID. A longitudinal study among patients in Wuhan with the original SARS-CoV-2 strain reported symptoms and the changing proportion of symptoms of long COVID at different follow-up time.[11] SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Vaccines against SARS-CoV-2 infection also offer protection against long COVID.[34–36] Krishna et al[37] reported a reduction in long COVID referrals at a teaching hospital in the UK over time, which is possibly correlated with reinfection and an increased rate of vaccination. Vaccinated people with breakthrough SARS-CoV-2 infection exhibited a lower risk in death during the acute phase and lower incident post-acute sequelae.[38]

The mechanisms of long COVID are unclear. Leading hypotheses include alteration of the immune system, the persistence of residual viral components driving chronic inflammation, endothelial dysfunction or activation, microembolization, mitochondrial dysfunction, abnormal metabolites, reactivation of pre-existing chronic viral infection,[39] dysbiosis of microbiota, and unrepaired tissue damage.[40] These hypotheses intersect and overlap. We summarized the common symptoms and possible mechanisms of long COVID in Fig. 2, which are discussed in detail in the following sections.

Alteration of the immune system

Patients with long COVID have an immune system that is in constant high alert.[2] Changes have been observed in both the SARS-CoV-2-specific adaptive and non-specific innate immune responses of patients with long COVID. Alterations of autoreactive immune responses have also been found. The primary findings are discussed below.

Adaptive immune cells in circulation

The adaptive humoral and cellular immune response against SARS-CoV-2 functions in viral clearance. Immune memory persists after infection to further protect the host, with virus-specific neutralizing antibodies and T-cell responses found up to 12 months post infection.[41] In contrast, a compromised immune response may lead to prolonged chronic immune activation and possibly long COVID. Studies have found that low perforin expression in CD8 + T lymphocytes during the acute phase of severe SARS-CoV-2 infection predicts long COVID.[42]

Alteration of the adaptive immune response also persists during recovery from acute infection. In a longitudinal study of patients with COVID-19, T-cell subsets exhibited different severity- and time-dependent dynamics.[43] An exhausted (PD-1-expressing)/senescent (CD57-expressing) state in CD4+ and CD8+ T cells and perturbance in CD4+ regulatory T cells were found in convalescent patients with long COVID at 3-month follow-up during recovery from severe disease. The exhausted/senescent state was still noted in CD8+ T cells up to 6 months after severe infection. Together with a decreased naïve cell population and augmented granzyme B and interferon gamma (IFN-γ) production, this suggests unresolved inflammation during long COVID.[43] Another cohort study also reported high antiviral cytotoxicity in CD8+ T cells and higher expression of exhaustion marker PD-1 in individuals with long COVID, as compared with patients who had completely recovered, corresponding to a state of chronic inflammation.[44] The spike-specific clonal CD4+ T-cell receptor β depth was significantly associated with both dyspnea and the number of symptoms at 12 months, suggesting that infection-induced SARS-CoV-2-specific immune responses might influence long COVID.[45]

The immunopathological features of long COVID in children differ from those of adults. Buonsenso et al[46] found that children with long COVID had a compromised ability to switch from the innate to the adaptive immune response, and these children showed a contraction of naïve

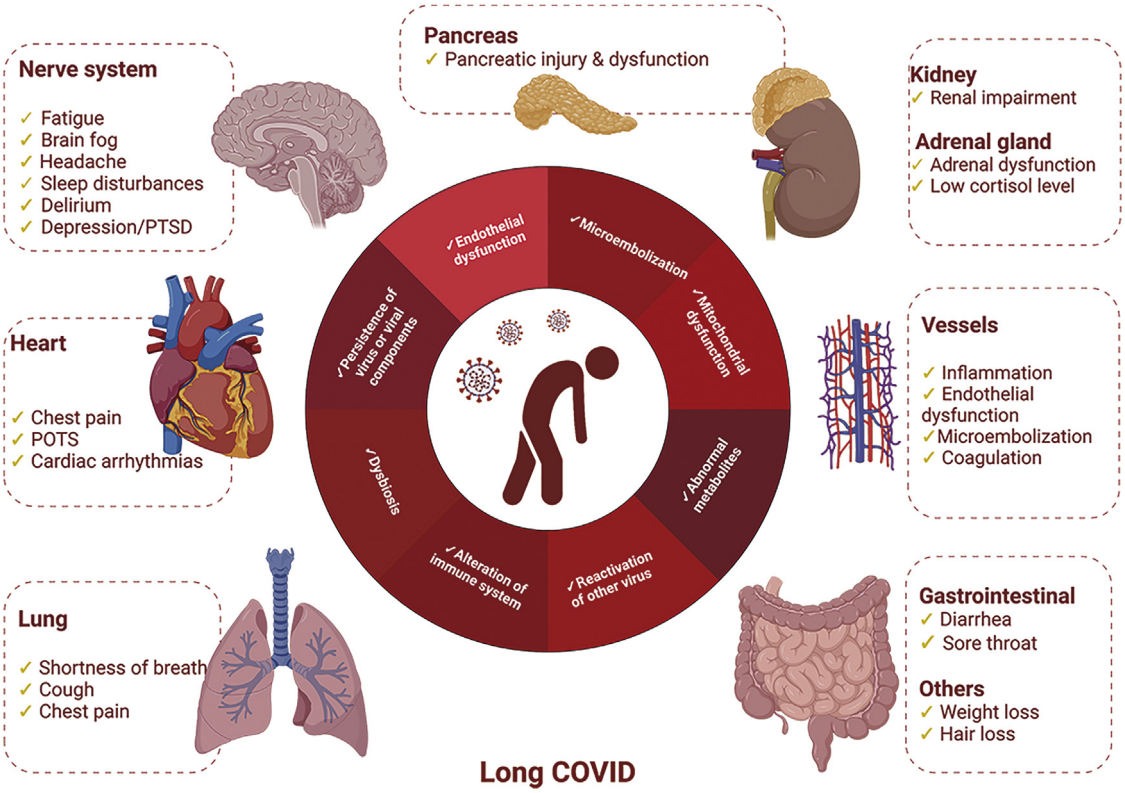

Fig. 2. Common symptoms and possible mechanisms of long COVID. POTS: Postural orthostatic tachycardia syndrome; PTSD: Post-traumatic stress disorder.

and switched B-cell compartment and an unstable balance of regulatory T lymphocytes.

Innate immune cells in circulation

The frequency and function of innate immune cells are also related to long COVID. Monocytes have been found significantly increased in frequency among patients with severe infection compared with those who had mild-to-moderate infection at 1–3 months post recovery, and these exhibited higher activation upon *in vitro* stimulation. However, the human leukocyte antigen (HLA) class II marker HLA-DR was found to decrease significantly, suggesting suppressed antigen-presenting function in patients post COVID-19.[47] Increased monocytes may be associated with worse disease severity, but the subsets of monocytes differ slightly.[48] Natural killer (NK) cells play a crucial role in controlling viral infection primarily via cytotoxicity and secretion of IFN-γ cytokine. NK cells are significantly increased in the peripheral blood of patients with long COVID in comparison with healthy controls.[47] CD59 ^{high} NK cells are decreased in subgroups with severe infection and are associated with increased pro-inflammatory cytokines, especially interleukin 6 (IL-6), which impairs the expansion and function of NK cells.[47] The myelopoiesis cytokines granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor were found to be higher in patients with long COVID compared with healthy controls. At one month after infection, high serum levels of IL-17 and IL-2 and low serum levels of IL-4 and IL-10 appear to constitute a cytokine profile of long COVID.[49] These markers are potential targets for long COVID treatment and prevention strategies. Mast cell activation symptoms are also increased in patients with long COVID.[50,51] A longitudinal cohort study, comparing the immune status and changes on lung computed tomography (CT) in patients with COVID-19, showed no significant difference in immune-related indexes compared with healthy controls at 1-year follow-up. However, in the abnormal CT group, complement C3 remained at a high level.[52]

Autoimmune response

Beyond abnormal immune cells and cytokines, autoimmune reactive inflammation is hypothesized to be one cause of long COVID.[53] The autoimmune response is associated with the release of autoantigens by activated or dying neutrophils, elevation of the neutrophil-to-lymphocyte ratio, and neutrophil extracellular traps. Persistence of neutrophil extracellular traps and anticardiolipin autoantibodies has been found in patients during the post-acute phase of COVID-19 infection.[54] Wang et al[55] used a high-throughput autoantibody discovery technique to screen a cohort of 197 patients with COVID-19 for autoantibodies against 2770 extracellular and secreted proteins. The authors found that these patients exhibited dramatic increases in a wide range of autoantibody reactivities, compared with uninfected controls.[56] We and others have also shown that antibody against anti-melanoma differentiation-associated gene 5 is prevalent in patients with COVID-19, and a high titer of this antibody is correlated with severe disease and unfavorable outcomes.[57] A recent German study of 96 patients reported antinuclear antibody (ANA) titers ≥1:160 in 43.6% of patients at 12 months after COVID-19 symptom onset, and these patients had significantly higher proportions of neurocognitive symptoms.[58] Another study showed that post-acute COVID-19 symptoms are common among COVID-19 patients with rheumatic disease.[59] However, this correlation between long COVID and autoimmunity is uncertain. A cohort study showed that only 4.3% patients had higher ANA titers at 8 months after infection, which is lower than the frequency of ANA positivity in the general population (5%).[60] Another study found that anti-calprotectin antibodies were associated with a return to healthy status at 8 months post infection and may play a protective role in the pathology of long COVID.[61] Similarly, IFN-specific autoantibodies have been implicated in severe COVID-19[62–64] and have been proposed as a potential driver of the persistent symptoms characterizing long COVID[65]; however, a cohort study with 215 convalescent participants with SARS-CoV-2 infection showed that persistent anti-IFN antibodies were unlikely to contribute to long COVID symp-

toms.[66] These interesting findings suggest that the geographic distribution and sociodemographic characteristics of patient populations might account for the different results; thus, further studies are warranted.

Local immunity in organs

The above results are mainly based on studies involving patients' blood samples, but the immune responses in local tissues or organs may differ from those in circulation. Because acquisition of patient specimens is very difficult, few data on tissue or organ immunity are available.

The lungs comprise a special organ in that they are connected to the outside of the body via the airway, and many kinds of resident immune cells in the lungs play important roles in COVID-19 and long COVID.[67] Tissue-resident lymphocytes remain within the respiratory tract after clearance of the primary viral infection and provide immediate and superior immunity against reinfection with the same virus.[68,69] Dysregulated resident T cells have been shown to be associated with lung inflammation, pathology, and fibrosis after respiratory viral infection, particularly in older patients.[70] The airway and alveolar immune system or immune cells are also associated with long COVID. Vijayakumar et al[71] studied blood and bronchioalveolar lavage fluid (BALF) samples collected from individuals with ongoing post-COVID-19 respiratory disease, and they analyzed immune cell profiling and protein levels using flow cytometry and proteome analysis. The researchers found significantly more cells in BALF samples from patients post COVID-19 and that neutrophils, alveolar macrophages, T cells, and B cells were significantly increased in individuals post COVID-19, even 80 days after primary infection. The proteomes in BALF collected from patients post COVID-19 were different from those of healthy individuals, although the proteomes in serum returned to normal. Changes in lung local immunity, including elevated concentrations of proteins involved in epithelial dysfunction, tissue repair, and apoptosis, declined overtime.

Coagulation abnormalities and endothelial dysfunction

Abnormal coagulation and intravascular thrombosis are known landmarks of many forms of severe COVID-19 and have been associated with a higher risk of death. Persisting platelet activation and hyperactivity are present in COVID-19 survivors.[72] Elevated D-dimer is also reported in patients with long COVID, which raises the possibility of thromboembolic disease in long COVID.[73] Pretorius et al[74] used proteomics and fluorescence microscopy to study plasma samples from healthy individuals, individuals with acute COVID-19 and type 2 diabetes mellitus, and individuals with long COVID. The investigators found large anomalous (amyloid) deposits (microclots) in plasma samples from patients with long COVID. These microclots included various inflammatory molecules and α 2-antiplasmin, various fibrinogen chains, and serum amyloid A. Heparin-induced extracorporeal low-density lipoprotein (HELP)/fibrinogen precipitation apheresis, a kind of treatment that has been used for septic multi-organ failure, has been used for patients with acute COVID-19 or long COVID.[75] Some patients with long COVID have travelled to other countries to receive HELP and triple anticoagulation therapy, which have not been assessed using modern scientific methods; however, most of these patients did not meet the criteria for taking these anticoagulant drugs and had a high risk of bleeding.[76] Additional studies are required to validate the general applicability of HELP or anticoagulant drugs as a treatment for long COVID.

Routine coagulation parameters such as D-dimer,[77] von Willebrand factor (VWF), and factor VIII (FVIII) have been used as markers of endothelial activation and are also assessed in adults with long COVID. VWF antigen, VWF propeptide, and FVIII are significantly elevated in patients with long COVID, compared with controls.[78] Mounting evidence suggests that endothelial cells (ECs) are a direct or indirect preferential target of SARS-CoV-2 and that dysfunction of the endothelium is key in COVID-19.[79] Delayed catastrophic thrombotic events, vascular injury, and endothelial dysfunction have been found in post-acute COVID-19.[80,81] Endothelial dysfunction has a relationship with microvascular occlusion in patients with COVID-19; a significant decrease in vascular density was found in a prospective, observational cohort study of patients with long COVID.[82,83] An *in vitro* study investigating the effects of patient sera on ECs suggested a pro-angiogenic effect in serum from patients with post-COVID-19 syndrome as a compensatory mechanism for endothelial dysfunction, which is absent in patients with long COVID.[84] Thus, chronic endothelial dysfunction may play a role in long COVID, which might explain several of the key symptoms involving multiple organs.[85,86] Blood biomarkers for vasculature transformation are significantly elevated in long COVID, with angiogenesis markers (angiopoietin-1/P-selectin) yielding a classification accuracy for long COVID of 96% of the samples,[87] which has the potential for diagnostic and therapeutic applications. Endothelial biomarkers (endothelin 1 and angiopoietin-2) have also been found to alter in patients with post-COVID-19 syndrome.[88] During long COVID, there is ongoing endothelial cell dysfunction, dysregulated angiogenesis, as well as imbalance of the VWF and a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13 axis. Immunophenotyping has revealed significantly elevated intermediate monocytes and activated CD4+ and CD8+ T cells in convalescence, which are correlated with thrombin generation and endotheliopathy markers, respectively, showing cross talk between ECs and immune cells.[89] L-arginine and vitamin C can regulate endothelial dysfunction and oxidative stress,[90,91] and some studies show the favorable effects of these drugs in patients with long COVID.[90,92]

EC dysfunction and abnormal D-dimer are also associated with long COVID in children, and children with a more severe spectrum of disease, characterized by three or more persisting symptoms, had higher D-dimer levels than those who fully recovered from COVID-19. However, VWF, FVIII, VWF ristocetin cofactor, and fibrinogen showed no significant differences.[86]

Persistent presence of virus or viral components

Persistent existence of viral ribonucleic acid (RNA), protein, or whole virus could be the cause of autonomic dysfunction, independent of hospitalization status and severity of acute COVID-19 illness.[93] Occult viral persistence is another major underlying pathophysiological mechanism in long COVID.[94] SARS-CoV-2 RNA can be found in the feces,[95,96] plasma, and urine of patients with COVID-19[95] up to 7 months after infection. In another study, persistence of residual antigen and SARS-CoV-2 RNA was found in tissues (the appendix, skin, and breast) of patients with long COVID.[97] In addition to persistent virus and RNA, a common set of autoantigens is recognized in individuals post COVID-19.[61] Persistent circulating SARS-CoV-2 spike protein can be detected in the plasma of patients with long COVID up to 12 months after infection, which is thought to be associated with long COVID.[98] Moreover, the long-term level of anti-spike immunoglobulin G is associated with the breadth of autoreactivity post COVID-19.[61]

Mitochondrial dysfunction

Mitochondria play a central role in the host response to viral infection and immunity, functioning as a platform for immune signaling by engaging the IFN system. Mitochondrial double-stranded RNA triggers antiviral signaling, including in COVID-19.[99] The clinical presentation of long COVID partially overlaps with post-viral fatigue syndrome, and several studies support the hypothesis that the disruption of mitochondrial metabolic pathways is a possible cause of long COVID.[100,101] Miller et al[102] found that SARS-CoV-2 infection can lower the expression of nuclear-encoded genes related to mitochondrial complex I,[103] which can explain the dysfunction of mitochondria. The loss of mitochondrial membrane potential, which indicates mitochondrial dysfunction, has been observed in leukocytes from patients post COVID-19.[104] Pozzi[100] analyzed the published RNA dataset of human peripheral blood

mononuclear cells and found that SARS-CoV-2 infection affected the metabolism of small mitochondrial RNAs without altering overall mitochondrial transcription. Another study on the plasma metabolic phenotype showed that PASC plasma metabolites are indicative of altered fatty acid metabolism and dysfunctional mitochondria-dependent lipid catabolism.[105] These metabolic profiles obtained at rest are consistent with previously reported mitochondrial dysfunction during exercise and may pave the way for therapeutic intervention focused on restoring mitochondrial fat-burning capacity.[106] Understanding of mitochondrial dysfunction post SARS-CoV-2 infection may help in improving the understanding of long COVID-19 and resulting multi-organ dysfunction such as cardiovascular disorders,[107] as well as selective neuronal mitochondrial targeting in SARS-CoV-2 infection, which affects cognitive processes to induce "brain fog" in long COVID.[108]

Gut microbiota

Persistent SARS-CoV-2 RNA can be found in the feces of patients with long COVID, as previously mentioned. Recent studies have shown that gut dysbiosis is linked to the severity of COVID-19 and persistent complications months after disease resolution. In a prospective study, Su et al[109] used short-gun metagenomic sequencing to determine long-term alterations in the gut microbiome of patients with COVID-19. They found that gut dysbiosis in 78.7% of patients with PASC had not fully recovered with an average of 14-month follow-up. In another study, Liu et al[110] conducted multi-kingdom gut microbiota analysis and found that cluster 1 (characterized by a predominance of *Ruminococcus gnavus*, *Klebsiella quasipneumoniae*, *Aspergillus flavus*, *Candida glabrata*, *Candida albicans* [*C. albicans*], Mycobacterium phage MyraDee, and Pseudomonas virus Pf1) was significantly associated with severe COVID-19 and the development of PASC, which indicates that multi-kingdom microbiota may serve as a prognostic tool in patients with COVID-19. Published reports suggest the potential role of an altered gut microbiome in the gut–brain axis and associated neurological sequalae because altered gut microbiota cause increased expression of various mediators. For instance, zonulin causes disruption of tight junctions and stimulates the enteric nervous system and signals to the central nervous system (CNS), precipitating neurological sequalae in long COVID.[111]

Unrepaired tissue damage in different organs or systems

Lung

Respiratory symptoms, including shortness of breath, dyspnea, and fatigue, are the most common symptoms of long COVID, with dyspnea present in as many as 13.4% of survivors 2 years post infection.[112] We and others have reported persistent impaired pulmonary function and abnormal lung CT findings in COVID-19 survivors.[8,113–115] Positron emission tomography–computed tomography (PET-CT) has also revealed abnormal metabolism in the lungs and brains of patients with long COVID, in comparison with healthy controls.[116–118] The mechanism of persistent lung injury in long COVID is unclear, and relevant human studies are lacking. One hypothesis is that long COVID is associated with impaired endothelial function.[119] In patients with long COVID, signs of lung fibrosis is associated with activation of the absent in melanoma 2 (AIM2) receptor in circulating cells and the release of IL-1α, IFN-α, and transforming growth factor beta.[120]

Cardiovascular system

COVID-19 can lead to long-term severe post-COVID myoendocarditis, which is characterized by prolonged persistence of coronavirus in the cardiomyocytes, endothelium, and macrophages (up to 18 months) in combination with high immune activity.[121] Postural orthostatic tachycardia syndrome is another sequela of COVID-19,[122] but the cause is unclear. Direct viral damage, autonomic nerve damage, and brainstem injury might be related to this symptom. In a cohort study of patients recovering from COVID-19, cardiovascular magnetic resonance imaging (MRI) revealed cardiac involvement in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%). These findings were highly prevalent regardless of pre-existing conditions, overall course and severity of the acute illness, and time from the original diagnosis.[123] Arterial wall stiffening, endothelial dysfunction, and a persistently high oxidative burden might contribute to cardiac dysfunction in long COVID.[124,125] Long-term follow-up of patients with COVID-19 reveals a higher prevalence of hypertension and an increase in mortality following hospital discharge.[126] The PROLUN (Patient-Related Outcomes and Lung Function After Hospitalization for COVID-19) study demonstrated right ventricular and left ventricular diastolic dysfunction in approximately 50% of patients post COVID-19; among these, 27% of patients still had arrhythmias 3 months after infection.[127] Arrhythmogenic right ventricular cardiomyopathy presents with right ventricular dysfunction and arrhythmias and is associated with anti-desmoglein-2 (DSG2) antibodies. In serum samples of patients with long COVID, a high frequency of anti-DSG2 antibodies is found, which is related to cardiac sequelae.[128]

Kidney

The expression of angiotensin-converting enzyme 2 (ACE2) in the kidney is higher than that in the lung. Therefore, it is hypothesized that SARS-CoV-2 may infect the kidney and induce acute kidney injury. Although creatinine can return to normal in most patients following recovery from acute infection, several studies in different countries have shown that the kidney function of patients with long COVID may not completely recover.[7,129] A study from Shenzhen, China showed that a decrease in the glomerular filtration rate was still present 2 years after infection with SARS-CoV-2 wildtype virus.[12] Lipid mediators have a potential role in causing renal injury and fibrosis in long COVID.[130] Jansen et al[131] reported that SARS-CoV-2 directly infected kidney cells, led to increased collagen 1 protein expression, and was associated with increased tubule-interstitial kidney fibrosis in patient autopsy samples and in a human-induced pluripotent stem cell-derived kidney organoid. These could explain both acute kidney injury in patients with COVID-19 and the development of chronic kidney disease in long COVID. Post-COVID-19 patients with long COVID are at heightened risk for acute kidney injury or chronic kidney disease (CKD), and these conditions further increase their mortality risk.[132] The multi-ligand receptor for advanced glycation end-products (RAGE) and its ligands are contributing factors in CKD and COVID-19, as these two diseases promote RAGE activity. The downstream effects include inflammation, cellular dysfunction, tissue injury, and fibrosis. Interventions to reduce RAGE and RAGE ligand levels may offer novel approaches to protect kidney function in long COVID.[132]

Central and peripheral nervous systems

SARS-CoV-2 spreads to the brain via either the nasal cavity or blood stream and may trigger neuroinflammation.[5] The remaining sequelae of long COVID may occur as a result of acute neurologic complications such as stroke, encephalitis, and Guillain–Barré syndrome or other factors related to hospitalization such as delirium.[94,133–135] The pathophysiology of other neurological symptoms, such as cognitive or mental disorders, headache, and olfactory/gustatory dysfunction, could differ from the acute phase. The role of sustained neuroinflammation in the onset of symptoms has been hypothesized in many studies to involve microglia activation, autoimmunity, or local microthrombosis or mitochondrial dysfunction.[94] Autopsy studies of patients with long COVID and studies using a hamster model of long COVID could provide evidence regarding persistent neuroinflammation and microglia activation in the brain.[136,137] MRI in patients with long COVID reveals structural

alterations in the brain, such as significantly enlarged gray matter volume (GMV) in several clusters (spanning frontotemporal areas, the insula, hippocampus, amygdala, basal ganglia, and thalamus in both hemispheres) compared with controls, and GMV alterations in limbic and secondary olfactory areas are present in patients with long COVID, which might be dynamic over time.[138] Brain MRI can show changes to the structure of the brain, but it cannot show the metabolic changes before structural changes occur, as in PET.[117] Brain ^{18}F-FDG PET imaging has shown that outpatients with post-COVID-19 conditions exhibited extensive hypometabolic right frontotemporal clusters. Patients with more numerous symptoms during the initial phase and with a longer duration of symptoms were at higher risk of persistent brain involvement.[139] Another study showed that brain PET hypometabolism in patients with long COVID, involving the olfactory gyrus and connected limbic/paralimbic regions, extended to the brainstem and the cerebellum.[116] PET-CT in children infected with SARS-CoV-2 has shown hypometabolism in the left orbito-frontal region, which can explain neurocognitive symptoms in children with long COVID.[140,141]

Clinical symptoms of long COVID, including fatigue, myalgia, insomnia, headache, depression, and shortness of breath, can be explained by brainstem dysfunction induced by the tropism of SARS-CoV-2 and chronic inflammation during long COVID.[142] Both direct and indirect virus damage is associated with brainstem dysfunction. Because the ACE2 receptor is highly expressed in the brainstem compared with other brain regions, SARS-CoV-2 may persist in the brainstem.[142] Indeed, autopsy studies have found SARS-CoV-2 RNA and proteins in the brainstem.[143] Other brain autopsy studies in patients who died owing to COVID-19, and where brainstem damage was observed, detected no SARS-CoV-2 RNA or protein; this result suggests that pathological immune or vascular activation also contributes to brainstem damage.[144]

SARS-CoV-2 infection increases the gene expression profile for Alzheimer disease risk in both an aged MA10 (mouse-adapted strain of SARS-CoV-2) animal model and in human patients.[145] A study in Finland suggested that the Apolipoprotein E4 (APOE4) gene is a risk factor for severe COVID-19 and post-COVID mental fatigue.[146] The ε4 allele of APOE4 is the strongest genetic risk factor for sporadic Alzheimer disease, which may be one reason why COVID-19 is a risk factor for Alzheimer disease.[147] SARS-CoV-2 S1 spike proteins contain both self-associating “prion-like” regions,[148] as well as amyloid peptide-binding and other domains that appear to play roles in pathological “seeding” amyloid genesis and/or spreading that supports the formation of pathogenic lesions in the brain and CNS, which contribute to pro-inflammatory neurodegeneration, neural cell atrophy, and/or neuronal cell death.[149]

In addition to the CNS, the activity of autonomic nerves (vagal) is impaired in patients with long COVID.[150] A cross-sectional study found that long COVID is also associated with psychiatric disorders, new onset psychiatric disorders, and suicide risk.[151] Autonomic nervous system damage could contribute to the symptoms of long COVID, without clear evidence of organ damage.[94]

Reports of anosmia are observed in acute COVID-19 and could be a unique symptom. Lechner et al[152] conducted a prospective, multi-center study consisting of baseline psychophysical measurement of smell and taste function in patients with COVID-19. A total of 218 individuals with a sudden loss of the sense of smell that continued for at least 4 weeks were recruited, and 76 individuals completed a 1-year follow-up. Of these, 52.6% (10/19) with an abnormal baseline Brief Smell Identification Test scored below the normal threshold at 1 year, and 82.8% (24/29) of them had persistent parosmia. Animal and human autopsy studies have suggested mechanisms of anosmia in acute COVID-19, such as destruction of the olfactory neuroepithelium or transmission of pathogens directly via the olfactory nerve in olfactory disorders.[153,154] The sense of smell is mostly recovered within 2 weeks or after other symptoms are improved. However, this could take longer in some patients with long COVID[155] and there is no significant difference after infection with different variants.[156] Hamsters infected with SARS-CoV-2 had prolonged inflammation in the olfactory system and various brain regions, including the striatum and cerebellum. This inflammation was evident in the absence of infectious virus and was associated with behavioral changes.[136] Recent studies in patients with PASC who have anosmia show a dysregulated axis among immune cells, horizontal basal cells, sustentacular cells, and olfactory sensory neurons arising in the PASC hyposmia olfactory epithelium, inducing sensory dysfunction. Local lymphocyte populations expressing interferon-γ and $\gamma\delta$ T cell markers were present in the olfactory epithelium of patients with PASC, indicating interferon response and inflammation here.[155] Trace elements play important roles in viral infections, and an imbalance of important trace elements can accelerate SARS-CoV-2 neurovirulence and increase neurotoxicity, which could have a role in the nervous system damage of long COVID.[157]

Endocrine system

Adrenal dysfunction might be related to long COVID, with the symptoms of long COVID and chronic adrenal insufficiency having striking similarities.[158] In the Mount Sinai–Yale Long COVID study, cortisol levels of patients with long COVID were approximately half those of healthy controls, which was the most significant predictor of long COVID.[159–161] Low cortisol levels in long COVID may be associated with adrenal gland dysfunction induced by viral infection and ensuing cellular damage.[162]

A case-control study in Spain showed that diabetes was not a risk factor for experiencing long-term post-COVID symptoms.[163] Another study found that prediabetes mellitus seemed to be associated with an increased risk of severe COVID-19 and higher serum levels of IL-6 during the acute phase, without long-term worsening of sequelae.[164] However, new-onset diabetes can persist in the post-acute phase of COVID-19. Possible mechanisms include virus-induced ß-cell cytotoxicity, insulin resistance, and dysregulation of the immune and renin–angiotensin systems.[165,166] Xie and Al-Aly[167] used the national databases of the US Department of Veterans Affairs to build a cohort of 181,280 participants who had a positive SARS-CoV-2 test between March 1, 2020 and September 30, 2021. They found an increased risk of diabetes in the COVID-19 group compared with a contemporary control group. One-year follow-up among patients in Wuhan post discharge showed that critical COVID-19 illness was associated with an increased risk of diabetes.[168]

Impaired lipid metabolism might be associated with long COVID, and body composition and nutrition may also be related.[169] Extreme obesity is a strong predictor of long-COVID in patients with severe COVID-19 illness and acute respiratory distress syndrome (ARDS).[170] A cross-sectional study of 50,402 patients with COVID-19 showed that obesity and lipid metabolism disorders determined the risk for development of long COVID syndrome.[171]

Musculoskeletal system

Musculoskeletal manifestations of COVID-19 are likely related to a hyperinflammatory host response, a prothrombotic state, or therapeutic effects rather than viral toxicity.[172] Physical inactivity and poor nutritional status are some mechanisms leading to muscle dysfunction in individuals with long COVID.[173] A case-control study showed that at 1 year post discharge from the intensive care unit, six patients with persisting dyspnea on exertion showed impaired volitional diaphragm function, although pulmonary function tests and echocardiography were normal. Diaphragm dysfunction with impaired voluntary activation can be present 1 year after severe COVID-19-induced ARDS and may be related to exertional dyspnea.[174] Low threshold provision of individualized nutritional and exercise interventions is important. In those most seriously affected by malnutrition and sarcopenia, ambulatory or inpatient rehabilitation should be considered. Geriatric rehabilitation programs should be specifically adapted to the needs of older patients with COVID-19.[175]

Epigenetics, single-nucleotide polymorphisms (SNPs), and other factors related to long COVID

A logistical study involving RNA-seq and whole-genome bisulfite sequencing of blood cells showed significant changes in both transcript abundance and DNA methylation of genes and transposable elements in patients who had recovered from COVID-19, identifying 425 upregulated genes, 214 downregulated genes, and 18,516 differentially methylated regions in total. These results support that an overactivated immune response, abnormal stress response, and metabolic processes are associated with long COVID.[176] Another study involving longitudinal DNA methylation profiling analysis found that the accumulation of epigenetic aging is associated with long COVID, which cannot be reversed at late clinical phases in some patients.[177] ACE2 and type II transmembrane serine protease (TMPRSS2) are receptors of SARS-CoV-2. The spike protein (S) of SARS-CoV-2 is a viral envelope glycoprotein that binds to ACE2 after its cleavage at sites S1/S2 by TMPRSS2. Findings differ regarding whether SNPs of ACE2 and TMPRSS2 are associated with long COVID. A cohort study of patients with long COVID showed a negative correlation between loss of taste and ACE2 gene expression levels.[156] Another study showed that the four SNPs of ACE2 were associated with COVID-19 severity; however, this did not predispose individuals to developing long COVID symptoms after recovery from COVID-19 infection during the first wave of the pandemic.[178] Luo et al[179] analyzed ACE2 SNPs in European and Chinese populations and found that the rs2106809 G allele significantly increased the expression of ACE2, and the ACE2 SNP rs2106809 was a functional brain expression quantitative trait locus and potentially involved in long COVID; these findings warrant further investigations. Reactivation after infection with other viruses may be associated with long COVID. One study showed that reactivation of Epstein–Barr virus (EBV) in the throat was more common in patients with long COVID fatigue than in convalescent patients with SARS-CoV-2 infection, suggesting that EBV replication may be a cofactor in a subgroup of patients who develop long COVID fatigue.[180]

Conclusion

Long COVID is a multisystem illness. The COVID-19 pandemic has been ongoing for over 3 years. On the basis of more than 3 years' research on long COVID, its mechanisms remain unclear, possibly due to the strict viral experimental conditions. Until now, the leading hypotheses regarding long COVID include alteration of the immune system, persistence of residual viral components driving chronic inflammation, endothelial dysfunction or activation, microembolization, mitochondrial dysfunction, abnormal metabolites, reactivation of pre-existing chronic viral infection, dysbiosis of microbiota, and unrepaired tissue damage.

Vaccination has been actively promoted in China and around the world. Additionally, multiple novel small-molecule anti-viral drugs have been developed against the virus. However, with the emergence of new variants (e.g., omicron) of SARS-CoV-2, the pandemic will not easily be resolved, and the situation remains challenging. Patients infected with the omicron variant generally have milder illness than patients infected with previous variants. Although we are gradually accumulating evidence regarding long COVID, whether omicron causes persisting symptoms and whether the mechanisms are similar to those of previous variants are still unknown. Much work remains to more clearly understand the mechanisms of long COVID.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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