

A Review of Neurological Symptoms in Long COVID and Clinical Management

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Abstract

Long COVID is a clinical diagnosis generally referring to the persistence or development of new symptoms, affecting multiple organ systems after SARS-CoV-2 COVID-19 infection. Long COVID is thought to affect ~20% of people after infection, including all age ranges and severity of infection. Fatigue, postexertional malaise, and respiratory and cardiac symptoms are commonly described. Neurological symptoms such as cognitive changes, sensory disturbances, headaches, and dysautonomia are common as well. The underlying pathophysiology remains unclear but immune dysregulation, autoimmunity, persistent viral reservoirs, and microvascular dysfunction have been implicated. As there are no tests at this time to diagnose long COVID, work-up should be focused on assessing reversible or treatable causes of symptoms. Furthermore, no treatments for long COVID currently exist, and management remains focused on a multimodal approach and symptom management, with many people showing improvement in symptoms over time.

Keywords

- fatigue
- brain fog
- dysautonomia
- headache
- neuropathy

Over 500 million people worldwide have had COVID-19.¹ While the initial focus was on the acute viral illness, it quickly became apparent that many people continued to experience long-term effects following infection. These long-term symptoms have come to be known as long COVID, long-haul COVID, post-COVID conditions, postacute sequelae of SARS CoV-2 infection, and many other names. The lack of consensus on a name highlights the complexity of this emerging condition and our growing understanding of what may cause these chronic symptoms.

Long COVID is defined as the persistence or development of new symptoms after initial COVID-19 infection.^{2,3} The Centers for Disease Control and Prevention (CDC) criteria state that symptoms should be present for at least 4 weeks after recovery from infection, whereas a World Health Organization (WHO) working group established a time frame of 3 months after acute infection has resolved. Symptoms often involve different organ systems, with many people experiencing multiple issues that may fluctuate, improve, or relapse over time. Among the many symptoms reported in long COVID, neurological issues have emerged as some of the

most frequent.⁴ As neurologists see increasing numbers of long COVID patients, the ability to recognize these symptoms early is critical. Diagnostic testing often does not provide answers² and can lead to delays in initiating management. While our insight into long COVID continues to evolve, many symptoms share similarities with known syndromes, which can provide guidance for clinicians. Here, we will review the literature to date on long COVID, the common neurological symptoms seen, and an approach to work-up and treatment.

Epidemiology

It remains unclear how many people will go on to develop long COVID, with studies showing anywhere from 4.7 to 80% of people having persisting symptoms after infection, and one large online survey of people with suspected or confirmed COVID-19 infection showed 93% reporting persisting symptoms 35 weeks later.^{4,5} Recent data from the U.S. Census Bureau estimated that 40% of adults in the United States had long COVID at some point and approximately 20% were still experiencing symptoms.⁶

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There are multiple factors that may contribute to the large variation in results, including different end points with some studies reporting on symptoms as little as 3 weeks after illness.⁵ For studies with longer end points that were initiated earlier in the pandemic, the predominant SARS-CoV-2 variant at time of infection may also affect prevalence. A recent study reported an odds ratio (OR) of developing long COVID with the omicron variant of 0.24 to 0.5 compared with delta, and thus earlier variants such as alpha may have different corresponding risks as virulence and transmission changed over time.^{7,8} Further complicating data from earlier in the pandemic is the lack of widespread polymerase chain reaction (PCR) testing at that time. As a result, earlier studies tended to focus on people who were hospitalized with confirmed SARS-CoV-2 testing. Studies looking at nonhospitalized people may include those with presumed COVID-19 infection but lacking confirmation given limited access to testing early in the pandemic.^{4,9}

Risk factors for long COVID also remain unclear, with contradictory findings in studies. One systematic review found that older age, female sex, more severe COVID-19 infection, and higher number of medical comorbidities at baseline were predictors for developing long COVID.⁵ Yet the U.S. Census Data showed that women and younger age were associated with higher risk.⁶ Furthermore, a Mediterranean cohort study found no baseline features to be predictors of developing long COVID.¹⁰ Some data have pointed to those reporting more than five symptoms in the first week of COVID-19 infection being more likely to develop long COVID (OR, 3.95; confidence interval [CI], 3.1–5.04)¹¹; however, other researchers have found that asymptomatic infection was a positive predictor.¹² The contradicting findings may be explained by differences in study populations, such as hospitalized patients tending to be older and with more medical comorbidities,^{13,14} which may make comparison with nonhospitalized patients difficult.

Beyond differences in methodology, disparities in results likely indicate that despite similar phenotypes among many people, long COVID is not a single disease entity but rather a heterogeneous group of conditions with overlapping symptoms. Commonly reported symptoms such as fatigue can have many different underlying etiologies depending on illness severity. A study of hospitalized patients 6 months after discharge found that those who had required supplemental oxygen beyond nasal cannula had an OR of 4.60 (95% CI, 1.85–11.48) for diffusion impairment abnormalities on pulmonary function testing and OR of 2.69 (95% CI, 1.46–4.96) for fatigue or muscle weakness, compared with those who had been admitted but not requiring oxygen. Fifty percent of patients with follow-up computed tomography (CT) imaging of their chest showed some abnormality, most commonly ground-glass opacities.¹⁵ Another study assessing patients 1 year after hospital discharge showed 35.4% with persisting fatigue, and within that cohort there was a new diagnosis of chronic obstructive pulmonary disease (1.8%) or heart failure (2%) within the year after discharge.¹⁶ These studies point to the potential of cardiopulmonary sequelae in

moderate-to-severe COVID-19 infection as one potential contributor for some people.

Post-intensive care unit (ICU) syndrome (PICS) describes the long-term effects of critical illness, which can include fatigue and cognitive changes.¹⁷ Studies focusing on people with severe COVID-19 and admitted to the ICU have found at 3-month follow-up that 87.5% had not recovered to baseline functional status and only 6.2% reported full subjective recovery along with normal scores on cognitive, mental health, and activities of daily living scales.¹⁸ In this group, fatigue could be explained by sequela of severe infection or PICS, which is not COVID-19 specific; however, not everyone who was hospitalized experienced end-organ damage,¹⁹ nor do any of these studies shed light on the cause of fatigue in people who had mild infection and no evidence of organ damage. This highlights the complex and multifactorial nature of long COVID, where prevalence and risk factors are likely to vary among different groups (→ Fig. 1).

Neurological Features of Long COVID

Fatigue

Fatigue and postexertional malaise (PEM) are often cited as the most common long-term issues regardless of initial COVID-19 severity.^{5,15,20,21} In several prospective studies of people recovered from COVID-19, fatigue was present in up to 49% of people 4 weeks later, and up to 40% showed severe enough disability that they were unable to return to work within several months.²² Fatigue can include both physical and/or mental exhaustion, and may be associated with myalgias or dyspnea. Often, it is accompanied by PEM—a worsening of symptoms 1 to 2 days after even mild physical or mental exertion.⁴ While the underlying cause of fatigue and PEM may be broad, they may also be indicators of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),²³ a disabling and poorly understood illness that

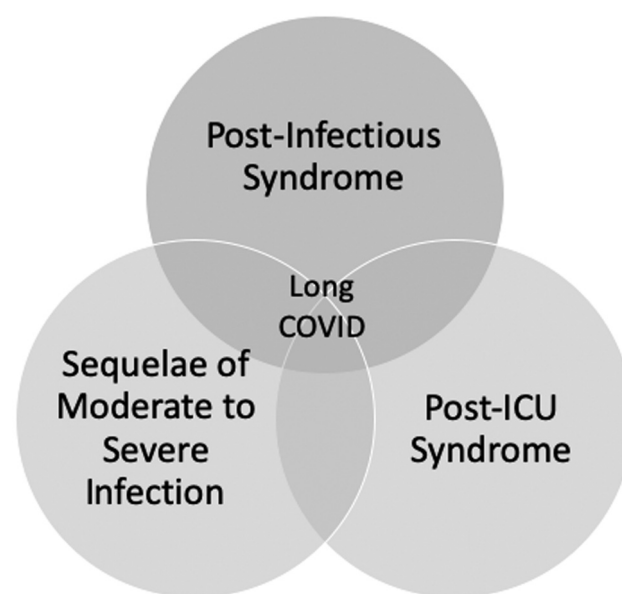


Fig. 1 Suspected overlapping etiologies of long COVID.

is often considered to be postviral in etiology and which shares many clinical similarities with long COVID.²⁴ The etiology of fatigue and PEM in ME/CFS and postviral conditions is not well known; it is thought to be due to complicated interactions between cellular metabolism, inflammation, and their effects on different organ systems.²⁵ While the underlying etiology of fatigue remains unclear and may not represent a solely neurological issue, many people will present to neurologists for these symptoms or associated issues such as cognitive changes and dysautonomia (discussed later), which often accompany the fatigue and can worsen in the setting of PEM.

Cognitive Dysfunction

Cognitive dysfunction has been reported in approximately 25% of people 12 weeks after COVID-19 illness.^{26,27} Commonly referred to as “brain fog,” the cognitive changes can encompass any number of domains including difficulty with memory, concentration, language, and executive dysfunction. In a cross-sectional study of 740 participants (mean age, 49 years [38–59]) presenting on average 7.6 months since COVID-19 diagnosis for cognitive testing, results showed deficits in memory encoding (24%), recall (23%), category fluency (20%), processing speed (18%), executive function (16%), and phonemic fluency (15%). In adjusted analysis, patients hospitalized with COVID-19 were more likely to have deficits in specific cognitive domains than those presenting to the emergency department or remaining outpatient.²⁸ Other studies have shown a correlation between cognitive dysfunction and overall illness severity, premorbid functional status, baseline comorbidities, and years of education in hospitalized patients.^{29,30}

Persisting cognitive dysfunction remains a common symptom for many people who were not hospitalized as well. In a prospective study of 100 patients (mean age, 43.2 ± 11.3 years) presenting to the Neuro COVID-19 Clinic at Northwestern University, 81% described some persisting cognitive changes, and the most common abnormal exam findings were impaired 4-item recall (32%) and serial 7s (27%). Those with PCR-confirmed COVID-19 infection showed significant impairment in attention and working memory on cognitive assessments.⁹

One of the most common concerns among patients with long COVID and cognitive dysfunction is whether they have dementia. While data remain limited, it does appear that older adults with severe infection have an increased risk of dementia. In a cross-sectional study from China of approximately 1,500 people, 10.5% of people with severe COVID-19 infection showed cognitive impairment consistent with dementia, compared with 0.69% in those with nonsevere infection ($p < 0.001$). They also found no significant difference in the proportion of cases with dementia or mild cognitive impairment in people with nonsevere infection compared with controls ($p = 0.703$ and 0.123 , respectively).³¹ A large retrospective review of electronic medical record diagnoses found a new diagnosis of dementia after COVID-19 in only 0.67%; however, when illness severity was taken into consideration, the frequency increased to 4.72% in

patients with encephalopathy.³² A recent retrospective review of over 6 million adults ≥ 65 years old found an increased risk of dementia after COVID-19 infection (hazard ratio, 1.69; CI, 1.53–1.72) and risk positively associated with increasing age and female gender.³³ While the preliminary data does show an increased risk of dementia in older adults, there is no data to date showing dementia in younger people, who often consist of a substantial proportion of people presenting with long COVID and cognitive concerns. The etiology of cognitive changes in younger people or those with mild COVID-19 infection remains unclear, but does not appear to be consistent with a clinical diagnosis of dementia.

One major challenge in understanding cognitive changes in long COVID is the lack of baseline cognitive testing and thus quantification of how current deficits represent a change from baseline. Several studies of nonsevere COVID-19 patients enrolled predominantly younger, educated patients,^{9,28} where subtle cognitive changes may be subjectively noticeable but not evident in test scores. In those cases, patients may report severe cognitive changes due to a large degree of change from baseline but still score within the normal range on tests. The role of contributing factors also remains poorly understood. Sleep disruptions, depression, and anxiety are all frequent symptoms reported in long COVID³²; however, many may report they are secondary to ongoing deficits and thus the degree of contribution to cognitive changes may be unclear.

Dysautonomia

The autonomic dysfunction in long COVID refers to a constellation of symptoms seen in many patients, including subjective feelings of lightheadedness/dizziness, palpitations, shortness of breath, gastrointestinal disturbances, and objective findings of labile blood pressure, tachycardia, orthostatic intolerance, and body temperature fluctuations. Often, these symptoms are associated with fatigue, cognitive dysfunction, and headaches, and may appear clinically similar to postural orthostatic tachycardia syndrome (POTS).³⁴ Given the overlap of many of these symptoms with other cardiovascular or neurological issues, it remains unclear how frequent dysautonomia occurs in long COVID; however, in one large cohort study, 19% reported receiving a diagnosis of POTS after having COVID-19.⁴ In the same study, prevalence of dizziness, tachycardia, and palpitations was 60 to 70%, highlighting the potential underdiagnosis of autonomic dysfunction.⁴ In a case series from Mayo Clinic of 27 patients with autonomic symptoms after COVID-19 infection, autonomic function testing (AFT) was abnormal in 63%. The primary symptoms were lightheadedness (93%) followed by orthostatic headache (22%), and 22% met criteria for POTS, with another 11% diagnosed as orthostatic intolerance. In the majority of cases, autonomic testing abnormalities were mild, highlighting that even minimal autonomic dysfunction can still cause noticeable impairment.³⁵ Dysautonomia may also play a role in the fatigue that many experience. In a study of long COVID patients with and without fatigue and a control group, there was a significant dissociation ($p = 0.046$) over time in autonomic testing

between long COVID patients with fatigue compared with controls, but not in the group without fatigue.³⁶ While a small study, the implications on the autonomic nervous system causing more widespread symptoms, as commonly seen in POTS, are commonly hypothesized, although the direct cause remains unclear.

The heterogeneity of symptoms seen in autonomic dysfunction can make a diagnosis challenging, and often these patients may be referred to multiple specialties. Obtaining a comprehensive history of all active issues and attempting to elucidate correlations among symptoms when possible is imperative when seeing these patients. A low threshold of suspicion for dysautonomia should be present in patients coming in for nonspecific gait changes or unsteadiness associated with other symptoms such as palpitations, even if they deny overt lightheadedness, and further testing may be beneficial.

Headache

Headache is one of the more common symptoms reported in acute viral illness,³⁷ as well as in long COVID, with reports between 44 and 91.2% of people experiencing some persisting headache.^{4,9,11,38} There is limited research focusing specifically on headaches and their characterization in long COVID. For some with a history of primary headache disorder, long COVID may present as a worsening in severity or frequency of their preexisting headache. Others with no history of headaches may report new headaches of varying phenotypes. Many may describe something akin to a new daily persistent headache (NDPH), which has been previously reported as sequelae of other viral infections.^{39,40} Headache may also be part of a larger syndrome such as ME/CFS or POTS, as it commonly clusters with other long COVID symptoms such as fatigue and brain fog.^{33,41} For others, headache may be the result of other issues such as sleep disruptions that have also been commonly reported in long COVID.¹⁵

There are limited data, but secondary headache disorders appear to be much less common. In a small cross-sectional study of 56 patients with acute COVID-19 infection and headache who underwent lumbar puncture, 46.1% met criteria for idiopathic intracranial hypertension (IIH) based on opening pressure, but only 2 people went on to require long-term treatment with acetazolamide after infection resolved.⁴² The study does not comment on risk factors for developing IIH in this cohort, and raises a question of risk in acute infection; however, given that only two people required continued treatment for IIH after infection and the lack of any other data showing IIH in long COVID, it does not appear to be a common diagnosis. Cerebral venous sinus thrombosis has been reported in acute infection as well as after vaccination for COVID-19, but there are limited data in long COVID.^{43,44} While the data remain sparse, secondary headache disorders appear relatively rare in long COVID.

Sensory Disturbances

Numbness, tingling, burning, and other abnormalities in sensation are also frequently described, with one study reporting 60% of patients having some subjective sensory

complaint.⁹ Localization of sensory abnormalities can vary widely, and includes distal extremities, focal, multifocal, or diffuse. Neurological examination may be normal, or show signs of a peripheral nerve process including decreased sensation to different modalities and reduced deep tendon reflexes.^{9,45} Small fiber neuropathy (SFN) has been implicated as a potential etiology of these sensory changes, and two case series have shown evidence of SFN in 63% and 46.2% of patients assessed.^{45,46} In one study, none of the patients had preexisting neuropathy risk factors, whereas the second study described several people with SFN risk factors that were well controlled. One patient with severe COVID-19 was diagnosed with critical illness axonal neuropathy and another with multifocal demyelinating neuropathy occurring 3 weeks after mild infection.⁴⁵ While there are other case reports of immune-mediated neuropathies such as Guillain-Barré syndrome occurring after COVID-19, this appears to be an infrequent presentation.⁴⁷ Of note, several patients in each study also showed abnormal AFT including absent or reduced sweat output on quantitative sudomotor axon reflex test, orthostatic tachycardia, and orthostatic hypotension.^{45,46} Sensory disturbances are frequently described in ME/CFS and POTS, and many with long COVID sensory abnormalities may describe clustering with other symptoms such as fatigue and dysautonomia, highlighting the role of the peripheral nervous system in ongoing symptoms.

Sleep Disruptions and Neuropsychiatric Symptoms

Since early in the pandemic, difficulty with sleep, anxiety, and depression have been commonly reported following COVID-19 infection. In a study of 1,733 patients who were discharged from the hospital, 26% reported sleep difficulties and 23% reported anxiety and depression 6 months later. Anxiety and depression positively correlated with more severe infection (OR, 1.77; 95% CI; 1.05–2.97).¹⁵ In a retrospective review of 236,379 electronic medical records of people with COVID-19 infection, 23.98% showed a diagnosis of mood disorder, with 8.63% having a first-time diagnosis, and 5.42% had a diagnosis of insomnia. The same study compared the risk of having these diagnoses after COVID-19 with influenza or other respiratory illnesses, and found a significant risk associated with COVID-19 ($p < 0.0001$ for both).³² A meta-analysis of long COVID found that sleep disturbances, depression, and anxiety were reported in 31, 17, and 23%, respectively. They also found that nonhospitalized patients were more likely to experience these symptoms 3 months later when compared with hospitalized patients; however, that trend reversed when studies included >20% patients admitted to the ICU.⁴⁸

The etiology of these neuropsychiatric changes is likely multifactorial, including general mental health effects of the pandemic on the public, trauma associated with COVID-19 infection, and, for those with severe infection, PICS.^{17,49} There is also a question of whether these symptoms are a direct consequence of SARS-CoV-2 infection/inflammation of the brain causing neuropathological changes⁵⁰; however, further research into this topic is needed. The effects of sleep and mood on other long COVID symptoms such as fatigue,

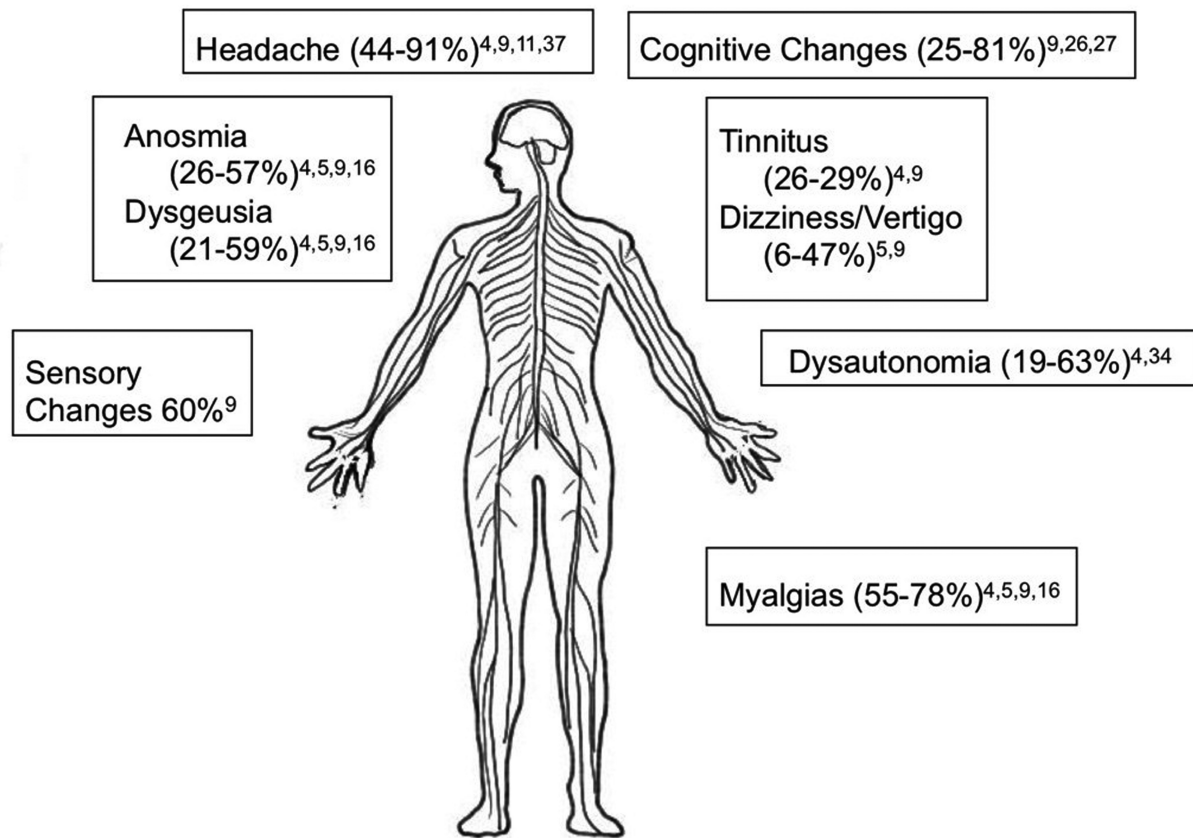


Fig. 2 Frequency of common neurological symptoms.

cognitive changes, and headaches remain one of significant importance; however, dismissing the widely reported symptoms in long COVID as merely the effects of neuropsychiatric issues is not fully supported by the evidence, nor is it clinically beneficial to patients when they seek help.

Other Neurological Symptoms

While the above-mentioned symptoms are often reported as the most frequent and potentially disabling in long COVID, there are a myriad of other issues that commonly occur. Anosmia and dysgeusia, both commonly seen in active infection,⁵¹ persist for many. Myalgias and other pain-related issues, vertigo, tinnitus, and tremor/abnormal movements are also commonly reported (► Fig. 2).

Potential Pathophysiology

Postviral syndromes have been well described in the literature and often have similar phenotypes to long COVID, including severe fatigue, musculoskeletal pain, cognitive difficulties, and neuropsychiatric symptoms.⁵² The severe acute respiratory syndrome (SARS) pandemic of 2003 led to substantial disability in many survivors, with one study showing 40.3% having chronic fatigue and 27.1% meeting criteria for ME/CFS an average of 3 years later.⁵³ To date there are little data to explain the underlying pathophysiology of long COVID, including its neurological effects; however, it is likely due to a range of overlapping and interacting factors.

Immune dysregulation from infection is frequently cited as a potential cause for many postviral syndromes, as well as ME/CFS. Infections may cause release of proinflammatory cytokines, alterations in B-cell populations and T-cell activation, and induction of autoimmunity, all of which can lead to persisting subjective symptoms of illness from infection.⁵⁴ Evidence of persisting changes in both innate and adaptive immunity of people recovered from COVID-19 infection could point to underlying dysregulation of the immune system⁵⁵; however, other studies have failed to show differences in cytokine profiles between long COVID patients and those who have fully recovered.⁵⁶ There is evidence to support chronic states of stress and inflammation triggering autonomic dysfunction, potentially through fluctuations in adrenergic tone,⁵⁷ which in turn may perpetuate chronic inflammation through vagal dysfunction and its effects on gastrointestinal function and the microbiome.⁵⁸

In the central nervous system (CNS), postmortem neuropathology studies of people deceased from COVID-19 infection have shown evidence of neuroinflammation, microglia activation, hypoxic/ischemic changes, and hemorrhagic or ischemic infarcts.^{59,60} While these studies were done on the most severely affected patients, they do highlight the potential for CNS damage that may have long-lasting consequences in other people. In a longitudinal neuroimaging study of 785 participants in the United Kingdom, 401 of whom tested positive for COVID-19 infection in between scans, magnetic resonance imaging showed a reduction in gray matter

Table 1 Overview of diagnostic testing

Test	Utility	Limitations
Bloodwork <ul style="list-style-type: none"> CMP, CBC, hemoglobin A1c, thyroid function, vitamin levels (e.g., B₁₂, D), ANA, CRP, ESR 	Assessing for reversible causes of symptoms	Abnormal values may be transient and part of long COVID process (i.e., ANA, CRP, ESR).
Neuroimaging	Diagnostic work-up for etiologies beyond long COVID	Unclear significance of nonspecific findings
Cognitive testing	Guide cognitive rehabilitation May provide reassurance correlating objective results with subjective symptoms	Lack of baseline testing and confounding factors may limit interpretation of results
Autonomic function tests	Assist diagnosis when unclear symptoms present Differentiate between subtypes of POTS	Results may be mildly abnormal or not meet formal diagnosis despite symptoms
EMG/NCS	Work-up if concerned for large fiber neuropathy	Negative in SFN
Skin biopsy	Diagnosis of SFN	May be negative May not change management focus
Sleep studies	Diagnosis of underlying sleep disorder contributing to symptoms	May be normal or with nonspecific findings
EEG	Work-up of symptoms concerning specifically for seizures	Unlikely to provide actionable results for general long COVID symptoms
CSF studies	Work-up of alternative diagnosis requiring CSF testing	Invasive procedure Unlikely to provide actionable results for long COVID

Abbreviations: ANA, antinuclear antibody; CBC, complete blood count; CMP, complete metabolic panel; CRP, C-reactive protein; CSF, cerebrospinal fluid; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; POTS, postural orthostatic tachycardia syndrome; SFN, small fiber neuropathy.

thickness in the orbitofrontal cortex and parahippocampal gyrus, evidence of tissue damage in areas connected to the primary olfactory cortex, and a reduction in overall brain size in those with COVID-19 infection compared with controls.⁶¹ In addition to structural changes, functional abnormalities have also been noted. A small study of 35 patients with long COVID and 44 controls utilizing ¹⁸F-FDG brain positron emission tomography found significant hypometabolism in the bilateral rectal/orbital gyrus, temporal lobe, brainstem, and cerebellum.⁶² The underlying etiology of these structural and functional changes remains unclear; however, immune dysregulation and microvascular dysfunction may play a role.⁶³

Diagnostic Studies

For now, long COVID remains a purely clinical diagnosis.² Certain tests can provide supporting information that may guide management strategies, but excessive testing should generally be avoided as it can delay time to treatment and may cause stress for the patient. In general, the best approach to making a diagnosis is obtaining a comprehensive history of symptoms, their timing in onset to a COVID-19 diagnosis (if known), how symptoms may correlate/cluster with each other, and assessing for any concerning symptoms or exam findings (“red flags”) that may warrant further work-up for an alternative process (► **Table 1**).

While not necessary for diagnosing long COVID, further testing can be essential for assessing reversible causes of symptoms and guiding treatment. Bloodwork should be checked when there is concern for SFN and/or cognitive changes. If checked, autoimmune tests such as antinuclear antibody titers may be elevated⁶⁴; however, interpretation of these findings in the setting of long COVID remains unclear, and persistently elevated titers should be further assessed for an underlying autoimmune condition. For cognitive symptoms, formal cognitive testing can be beneficial in quantifying deficits and guiding management strategies. AFTs may be helpful in confirming a diagnosis of dysautonomia. If POTS is present, AFTs can determine the specific form—primary or “partial dysautonomic” that is characterized by venous pooling and orthostatic hypotension, or “hyperadrenergic” that is characterized by orthostatic hypertension and tachycardia.⁶⁵ This differentiation can be critical in determining management, and may be difficult to discern without formal testing.

Peripheral nervous system evaluation with electromyography and nerve conduction studies will be normal in SFN.⁶⁶ Skin biopsy for intraepidermal density of nerve fibers can assist in a diagnosis of SFN but may not be available to all patients due to insurance or local resource limitations, and in the absence of targeted treatment strategies for long COVID SFN, pursuing this level of work-up should be determined on an individual basis and may not be necessary for many.

The role of neuroimaging in long COVID remains unclear. While studies have shown structural and metabolic changes,^{61,62} they often use modalities that are not clinically available and the overall significance of these findings on management remains unclear. For most patients, especially those who were not hospitalized, imaging of the brain may be normal, or show nonspecific signs such as microvascular ischemic changes or atrophy, which can be hard to interpret in the context of COVID-19 without prior imaging for comparison and unlikely to change management.^{9,67,68} In the absence of established guidelines on the topic, neuroimaging in long COVID is ultimately at the provider's discretion, but may not be warranted in most people. Neuroimaging should be obtained if there is a question of an alternative process, or if concerning clinical and/or exam findings are present.

Other ancillary studies may be useful on a case-by-case basis. Sleep studies can be beneficial for a wide range of symptoms when sleep disruption is a major complaint. Undiagnosed obstructive sleep apnea may play a role in fatigue, cognitive changes, and headaches and can be easily addressed.⁶⁹ There is limited evidence at this time on the prevalence of primary sleep disorders in long COVID, but disruption in sleep architecture that may not meet criteria for a specific diagnosis may still have effects and can provide a focus for management strategies.⁷⁰ Seizures do not appear to be a frequent finding in long COVID, but electroencephalogram should be performed if concerning symptoms are present.⁹ Lumbar puncture and cerebrospinal fluid (CSF) testing are likely not needed in most cases unless there is a concern for an alternative, treatable process. In acute COVID-19 infection, CSF may show non-specific inflammatory findings (e.g., lymphocytic pleocytosis and elevated protein) and, in some cases, evidence of autoantibodies, but there is no evidence at this time of widespread CSF abnormalities in long COVID.⁷¹ With further research, potential biomarkers may be found in the blood and CSF, but until then, lumbar puncture is unlikely to provide actionable results in most.

Treatment

Many symptoms may improve on their own, and for people experiencing mild symptoms, time and reassurance may be sufficient. For people experiencing debilitating symptoms, managing individual or clusters of symptoms can provide relief and allow people to resume some daily activities. A multimodal approach is often needed to support patients in their recovery. This often entails participation in rehabilitation programs, pharmacological therapies for specific symptoms, and referrals to mental health services if psychiatric symptoms are present. In the following, we discuss management of the more common neurological symptoms.

Fatigue/Postexertional Malaise

Two of the most challenging symptoms to manage are fatigue and PEM. Underlying causes can be multifactorial, requiring an understanding of associated symptoms and often working

with other specialists to ensure respiratory, cardiac, and metabolic factors are also being managed. Rehabilitation programs are essential in managing long COVID fatigue and PEM; however, they must be tailored to meet individual needs. For patients with moderate-to-severe COVID-19 or PICS, early mobilization and exercise may be beneficial in counteracting the effects of deconditioning or neuromuscular complications acquired during prolonged hospital stays.^{72,73} However, deconditioning does not explain the vast majority of patients experiencing fatigue, and for many, exercise can lead to worsening symptoms (i.e., PEM), and aggressive rehabilitation strategies may pose more problems. Tests such as the 10 Meter Walk Test, 6 Minute Walk Test, or BERG Balance Scale may be used to evaluate overall exercise capacity and rehabilitation needs.⁷⁴ Comprehensive cardiopulmonary rehabilitation programs may provide benefit for many with long COVID and can be tailored to each person's needs and support overall functioning of daily needs.^{72,75}

For patients with PEM, discussing activity management or "pacing" is critical. Activities that trigger PEM may vary widely between people, so keeping symptom journals to better recognize what activities someone may tolerate and what triggers PEM can be helpful. From there, strategies can be developed to keep activities within the confines of what the patient can tolerate as much as possible, and scheduling frequent breaks for rest may prevent PEM. It is also critical to remind patients that they may experience "good days," where symptom burden is minimal, and may feel inclined to exert themselves further; however, this should be avoided as it will often trigger severe worsening of symptoms.⁷⁶

There are many studies looking at a variety of dietary options and supplements for treatment of fatigue, but no formal recommendations can be made beyond eating a balanced diet and addressing any underlying vitamin deficiencies that may contribute to symptoms.⁷⁶ Further research is also needed for pharmacological treatment of fatigue and PEM. Stimulants may be considered; however, given the risk for addiction, sleep disruption, and worsening anxiety or cardiovascular affects, they should be reserved for only the most severe cases, and careful monitoring is required.⁷⁷ In many cases where symptoms interfere with ability to work, accommodations at work or, in some cases, a medical leave of absence may be needed.

Cognitive Changes

Along with fatigue/PEM, cognitive changes can also prove to be challenging to manage. Cognitive rehabilitation, which provides skills for areas of deficits and compensatory strategies to improve cognition, may be beneficial for many people, although longitudinal data in long COVID are lacking. For some who experience cognitive changes as a type of mental fatigue along with physical fatigue and PEM, rehabilitation programs and pacing of activity as previously discussed may also help. For older adults, where there is concern that cognitive changes may represent an underlying neurodegenerative process, referral to cognitive specialists for further assessment and management may be prudent.

Potential contributing factors such as sleep impairment, depression, and anxiety should also be addressed given their frequency in long COVID and known effects on cognitive function.^{78–80} While these symptoms may be secondary to long COVID and perceived disability, they may still contribute to worsening symptoms and interventions may provide incremental improvement. However, it is important for providers to address depression and anxiety with compassion rather than dismissing them as the sole cause of long COVID, as that can lead to people avoiding care and may worsen feelings of stigma.⁸¹

Unfortunately, there are no proven medications for cognitive changes in long COVID at this time, and the mainstay of treatment remains focused on cognitive rehabilitation, mental health, and social support. Stimulant medications may be beneficial for some, but similar to patients experiencing fatigue, they should be reserved for those who do not benefit from more conservative management or have more severe cases that affect activities of daily living.⁷⁷

Dysautonomia

Patients with proven autonomic dysfunction by AFT and those with symptoms consistent with potential orthostasis can benefit from management strategies developed for POTS and autonomic neuropathy. Initial management should focus on removing any medications that may worsen autonomic dysfunction, increasing plasma volume with drinking at least 2 to 3 L of water daily, and increasing salt intake. Salt intake may need to be increased up to 10 to 12 g/day if tolerated, and salt tablets may need to be used.^{82–84} These interventions should be monitored by a medical professional and undertaken only if there are no preexisting contraindications such as congestive heart failure or kidney disease. In addition to measures to increase intravascular volume, compression garments that extend up to the lower abdomen should be used to limit venous pooling. Endurance exercise training has also been shown beneficial in reducing orthostatic symptoms. Results from a small randomized control trial showed improvement in 63% of participants undergoing specific training designed for dysautonomia, compared with 9% in the control group ($p = 0.008$).⁸⁵ In cases where pharmacological therapy is needed and hypovolemia is suspected to be the main cause, fludrocortisone or midodrine can be used. Low-dose beta-blockers may be useful in POTS for decreasing symptoms from tachycardia.⁸⁶ Pyridostigmine has shown positive effects in lowering the heart rate in POTS without effect on blood pressure; however, side effects from acetylcholinesterase inhibition may limit widespread use.⁸⁷ Recent data have also shown that ivabradine may be beneficial in managing hyperadrenergic POTS, with data from a randomized control trial showing significant improvement in heart rate ($p < 0.001$), physical ($p = 0.008$), and social functioning ($p = 0.021$) compared with placebo.⁸⁸

Sensory Changes, Neuropathic Pain, and Neuropathies

In cases where a mononeuropathy, immune-mediated neuropathy, or other etiology such as radiculopathy is found

to be the cause of sensory abnormalities, etiology-specific treatment should be undertaken according to appropriate guidelines. For sensory changes where the neurological exam is relatively normal or shows signs concerning for a distal sensory polyneuropathy, bloodwork should be checked for reversible causes of neuropathy and appropriate management of any abnormalities undertaken. When sensory disturbances are painful or bothersome, pharmacological treatment may be needed. Medications such as gabapentin, pregabalin, tricyclic antidepressants (e.g., amitriptyline, nortriptyline), and serotonin norepinephrine reuptake inhibitors (e.g., duloxetine and venlafaxine) can be beneficial.⁸⁹ The choice of individual medication should take into account patient comorbidities, concurrent medications, and side effect profiles. The role of immunotherapies such as corticosteroids and intravenous immunoglobulins for treating sensory disturbances or SFN remains unclear. In one small case series of long COVID sensory disturbances, 65% of participants received some immunotherapy. Fifty-two percent of all participants reported improvement in symptoms over time but none had complete resolution.⁴⁵ In the second case series of 13 patients, none of whom received immunotherapies, 1 was asymptomatic at 1-year follow-up, 8 reported some improvement with symptomatic medication management, and only 2 people had poorly controlled pain despite being on symptom management 8 to 11 months later.⁴⁶ Given the clinical course of long COVID involves improvement for some and fluctuations in symptoms for others, it is unclear if response to immunotherapy indicates treatment of the underlying etiology or the natural progression of symptoms.

Headaches

For all headaches, potential triggers such as caffeine intake, sleep, and hydration should be addressed. If adjustments to environmental factors do not improve headaches, medication management may be needed and should be based on headache phenotype following established guidelines for primary headache disorders. Acute headaches may be treated with nonsteroidal anti-inflammatories or acetaminophen. Acute migraines that do not respond to over-the-counter medications may require triptans; however, these should be avoided in people with cardiovascular disease. Frequent headaches (occurring more than 6 days/month) require preventive treatment to avoid medication overuse headache, with some oral antiseizure, antidepressant, or antihypertensive medications with proven efficacy. Chronic migraine may respond to onabotulinumtoxinA injections or newer medications such as the gepants or calcitonin gene-related peptide antagonists.^{90,91} NDPH can be quite disabling and challenging to treat. In general, it is recommended to treat based on the predominant headache phenotype with the above-mentioned medications. In all cases where the headache proves to be highly refractory to common oral preventative medications, referral to a headache specialist for assessment of onabotulinumtoxinA injections, nerve blocks, and other interventional practices might be needed.⁹²

Research into Future Therapeutics

More targeted therapeutics are needed for those most disabled by long COVID. As discussed, immunotherapies are a major area of focus given concern for an underlying immune dysregulation/autoimmunity; however, there are limited data on their efficacy compared with symptomatic treatment and time.^{45,46} Another option with some promise is low-dose naltrexone (LDN)—an opiate receptor antagonist. At lower doses between 1 and 4mg, it may have immune-modulating effects. A recent study of 38 people using LDN found that at 2-month follow-up there was a significant reduction in pain and mood, and a trend to significance in improvement of fatigue and cognitive changes.⁹³ There currently are clinical trials looking into LDN plus nicotinamide adenine dinucleotide, coenzyme Q10, atorvastatin, cannabidiol, and various rehabilitation strategies as treatment for long COVID. Hopefully, in time, more treatment options will be available.

Conclusion

Long COVID is a complex clinical diagnosis, likely encompassing a heterogeneous group of entities with limited evidence on pathophysiology, risk factors, diagnosis, and treatment. While much research has been done in the last 2 years, intrinsic differences in study populations can limit comparison. However, symptom-based management can provide some improvement in disability for those severely affected, and for many people, time and reassurance may be the most important factors. Hopefully, as our understanding of this entity improves, our ability to not only treat but also prevent long COVID will improve.

Conflict of Interest

None declared.

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