Long COVID Syndrome: Clinical Presentation, Pathophysiology, Management

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Long coronavirus disease (COVID) syndrome is persistent symptoms and complications that occurs in at least 10% of severe acute respiratory syndrome coronavirus 2 infections. Symptoms associated with long COVID can vary widely from person to person but commonly include: fatigue, shortness of breath, chest pain or discomfort, joint pain, difficulty concentrating (brain fog), headache, loss of taste or smell, sleep disturbances, palpitations, persistent cough. Possible pathophysiologic theories are viral persistence, dysregulated immune response, autoimmune response, endothelial dysfunction, gut dysbiosis, damage to organs and tissues, neurological involvement, post-viral syndrome. Although current diagnostic and treatment options are insufficient, the management aim to alleviate symptoms, improve quality of life, and support recovery. The possible therapies and interventions that may be considered are symptomatic management, rehabilitation and exercise, respiratory support, cognitive and psychological support, sleep management, nutritional support, support groups and patient education, anti-inflammatory drugs, immuno-modulatory therapies. For patients enduring prolonged suffering from this long COVID syndrome, a multidisciplinary approach is essential for comprehensive management.

Keywords: Complication, Immune response, SARS-CoV-2 infection

Introduction

Long coronavirus disease (COVID) syndrome, also known as post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, refers to a condition in which individuals experience persistent symptoms and complications following the acute phase of a COVID-19 infection. Long COVID syndrome can affect individuals of all ages, including those who had mild or moderate initial COVID-19 symptoms [1].

About 10% (65 million) of COVID-19 infected people around the world have long COVID syndrome. The incidence is estimated at 10–30% of non-hospitalized cases [2], 50–70% of hospitalized cases [3], and 10–12% of vaccinated cases [4]. Long COVID is associated with the highest percentage of diagnoses between the ages of 36–50 years, and most long COVID cases are in non-hospitalized patients with a mild acute illness [5].

Clinical Presentation

The defining characteristic of long COVID syndrome is the persistence of symptoms for weeks or months after the acute phase of the illness has resolved. Symptoms associated with long COVID can vary widely from person to person but commonly include: fatigue, shortness of breath, chest pain or discomfort, joint pain, difficulty concentrating (brain fog), headache, loss of taste or smell,
Brain fog: Cognitive impairment, including problems with memory.
Loss of taste and smell: Persistent loss or alteration of the sense of taste.
Chest pain: Discomfort or tightness in the chest.
Joint and muscle pain: Aches, soreness, and weakness in the muscles and joints.
Headaches: Recurring headaches or migraines.
Breathlessness: Difficulty breathing or shortness of breath, even when lying flat.
Other symptoms: Dizziness, palpitations, gastrointestinal issues, and skin rashes.

**Table 1.** Common symptoms associated with long COVID syndrome

| 1.  | Fatigue: Profound and persistent exhaustion that can interfere with daily activities. |
| 2.  | Breathlessness: Difficulty breathing or shortness of breath, even with minimal physical exertion. |
| 3.  | Brain fog: Cognitive impairment, including problems with memory, concentration, and focus. |
| 5.  | Chest pain: Discomfort or tightness in the chest. |
| 6.  | Headaches: Recurring headaches or migraines. |
| 7.  | Sleep disturbances: Insomnia, disrupted sleep patterns, or excessive sleepiness. |
| 8.  | Loss of taste and smell: Persistent loss or alteration of the sense of taste and smell. |
| 9.  | Mood disorders: Depression, anxiety, or mood swings. |
| 10. | Other symptoms: Dizziness, palpitations, gastrointestinal issues, and skin rashes. |

Sleep disturbances, palpitations, persistent cough (Table 1).

The World Health Organization (WHO) defines a symptom that occurs within three months of COVID-19 confirmation and lasts more than two months as “long COVID-19.” The most common symptoms are fatigue, decreased vitality, and shortness of breath [6]. In Korea, a research team of Seoul National University Hospital followed 147 patients confirmed with COVID-19 for more than three months and 55.8% of them complained of long COVID-19 symptoms. The most common persistent symptoms were chronic fatigue (32.7%), memory loss (15%), olfactory disorders (14.3%), anxiety (9.5%), myalgia (7.5%), hypogeusia (6.8%), and dizziness (6.8%) [7].

Long COVID-19 increases adverse outcomes, with new-onset cardiovascular, thrombotic and cerebrovascular diseases, type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), dysautonomia, and postural orthostatic tachycardia syndrome (POTS). These symptoms can last for years, and new-onset ME/CFS and dysautonomia are expected to be lifelong.

**Pathophysiology**

The exact cause and pathophysiology of the persistent symptoms are not fully understood, and many studies are still in progress. Possible pathophysiology theories are viral persistence [8], dysregulated immune response [9], autoimmune response [10], endothelial dysfunction [11,12], gut dysbiosis [13], damage to organs and tissues [14], neurological involvement [15], post-viral syndrome [16,17] (Table 2).

Multiple studies have revealed multi-organ damage associated with COVID-19. In a 1-year follow-up study with 536 participants, examining the heart, lungs, liver, kidneys, pancreas and spleen, found that 59% had single-organ damage and 27% multi-organ damage [6].

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Risk factors potentially include female sex, type 2 diabetes, Ebstein-Barr virus reactivation, the presence of specific antibodies, connective tissue disorders, attention deficit hyperactivity disorder, chronic urticaria, allergic rhinitis, Hispanic

**Table 2.** Possible theories of long COVID syndrome

| 1.  | Viral persistence [8]: One theory suggests that the SARS-CoV-2 virus may persist in certain tissues or organs in some individuals, leading to ongoing low-level viral replication and chronic inflammation. This chronic inflammation could contribute to the long-lasting symptoms experienced in long COVID. |
| 2.  | Dysregulated immune response [9]: It is possible that long COVID syndrome is caused by an abnormal or prolonged immune response to the initial infection. This theory suggests that the immune system continues to produce an exaggerated inflammatory response, leading to the persistence of symptoms. |
| 3.  | Autoimmune response [10]: Another theory proposes that long COVID syndrome may be linked to an autoimmune response, where the immune system mistakenly attacks healthy tissues in the body. This autoimmune response could be triggered by the initial viral infection. |
| 4.  | Endothelial dysfunction: Circulatory system disruption includes endothelial dysfunction and subsequent downstream effects, and increased risks of deep vein thrombosis, pulmonary embolism and bleeding events [11]. Microclots, thrombosis, long-term changes to the size and stiffness of blood cells have also been found in long COVID, with the potential to affect oxygen delivery [12]. |
| 5.  | Gut dysbiosis [13]: Higher levels of Ruminococcus gravis and Bacteroides vulgatus and lower levels of Faecalibacterium prausnitzii have been found in people with long COVID, with gut dysbiosis lasting at least 14 months. Low levels of butyrate-producing bacteria are strongly correlated with long COVID at 6 months. Persisting respiratory and neurological symptoms are each associated with specific gut pathogens. |
| 6.  | Damage to organs and tissues [14]: COVVID-19 can cause damage to various organs, including the lungs, heart, kidneys, and brain. Multiple studies have revealed multi-organ damage associated with COVID-19. In a 1-year follow-up study with 536 participants, looking at the heart, lungs, liver, kidneys, pancreas and spleen, found that 59% had single-organ damage and 27% multi-organ damage. |
| 7.  | Neurological involvement [15]: SARS-CoV-2 has been shown to enter the central nervous system, and there is evidence of neurological symptoms in COVID-19 patients. It is hypothesized that long COVID symptoms could result from direct viral invasion or immune-mediated damage to the nervous system. |
| 8.  | Post-viral syndrome: Long COVID syndrome shares similarities with post-viral syndromes seen in other viral infections. By reactivation of underlying pathogens, including herpesviruses such as Epstein-Barr virus (EBV) [16] and human herpesvirus 6 (HHV-6) [17]. These syndromes are characterized by prolonged fatigue, muscle pain, and cognitive difficulties. It is possible that long COVID represents a similar post-viral syndrome triggered by SARS-CoV-2 infection. |
or Latino heritage, lower income and an inability to adequately rest in the early weeks after developing COVID-19 [18].

It’s important to note that these theories are not mutually exclusive, and it’s likely that multiple factors contribute to the development of long COVID syndrome. Ongoing research is focused on understanding the underlying mechanisms and developing effective treatments for this condition.

Management

Although there are no broadly effective treatments of long COVID syndrome, the management and treatment aim to alleviate symptoms, improve quality of life, and support recovery. Since long COVID syndrome encompasses a wide range of symptoms and affects individuals differently, a multidisciplinary approach involving various healthcare professionals may be necessary. The possible therapies and interventions that may be considered are symptomatic management, rehabilitation and exercise, respiratory support, cognitive and psychological support, sleep management, nutritional support, support groups and patient education, anti-inflammatory drugs, immunomodulatory therapies (Table 3).

Many strategies for ME/CFS are effective for individuals with long COVID, including pacing and symptom-specific β-blockers for POTS, low-dose naltrexone for neuroinflammation and intravenous immunoglobulin for immune dysfunction) and non-pharmacological options (salt intake, cognitive pacing, and elimination diets for gastrointestinal symptoms).

The treatment for long COVID syndrome focuses on managing the individual’s symptoms and improving their quality of life. This may include a multidisciplinary approach involving healthcare professionals such as primary care physicians, specialists, physical therapists, occupational therapists, mental health professionals, and rehabilitation specialists.

It’s important to note that the treatment approach for long COVID syndrome is highly individualized, and healthcare professionals will assess and tailor interventions to each person’s specific needs and symptoms.


Conclusion

Long COVID syndrome is a condition where individuals continue to manifest a variety of symptoms even after confirming a COVID-19 infection. Patients often experience prolonged difficulty in coping with the aftermath. While various mechanisms and risk factors have been suggested, there is still a lack of definitive evidence in certain areas. However, for patients enduring prolonged suffering from this long COVID syndrome, a multidisciplinary approach is essential for comprehensive management.

Conflict of interest

The authors declare no conflicts-of-interest related to this article.
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