



Review Article

pISSN 2092-8335 • eISSN 2733-5380
Keimyung Med J 2023;42(2):71-74
<https://doi.org/10.46308/kmj.2023.00269>

Received: December 4, 2023
Accepted: December 8, 2023

Corresponding Author:
DaeHyun Kim, MD, PhD
Department of Family medicine,
Dongsan Medical Center, Keimyung
University School of Medicine, 1035,
Dalgubeol-daero, Dalseo-gu, Daegu 42601,
Korea
Tel: +82-53-258-4175
Fax: +82-53-258-4171
E-mail: dhkim@dsmc.or.kr

© 2023 Keimyung University School of Medicine
© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Long COVID Syndrome: Clinical Presentation, Pathophysiology, Management

Yoon Jeong Cho¹, DaeHyun Kim²

¹Department of Family medicine, Daegu Catholic University School of Medicine, Daegu, Korea

²Department of Family medicine, Keimyung University School of Medicine, Daegu, Korea

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,

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.
4. Joint and muscle pain: Aches, soreness, and weakness in the muscles and joints.
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 pathophysiologic 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).

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 gnavus* 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]: COVID-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.

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.

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

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

Table 3. The management of long COVID syndrome

1. Symptom management: Treatment may involve addressing specific symptoms experienced by individuals, such as medications for pain relief, anti-inflammatory drugs, or cough suppressants. Depending on the symptoms, interventions like physical therapy, occupational therapy, or speech therapy may be beneficial.
2. Rehabilitation and exercise: Gradual and individualized exercise programs, guided by physical therapists or rehabilitation specialists, can help improve physical function, reduce fatigue, and enhance cardiovascular fitness [19]. Pulmonary rehabilitation programs may be recommended for individuals with respiratory symptoms.
3. Respiratory support: For individuals with persistent respiratory issues, interventions like supplemental oxygen, breathing exercises, and pulmonary rehabilitation may be employed to improve lung function and breathlessness [20].
4. Cognitive and psychological support: Brain fog, memory problems, anxiety, and depression can significantly impact individuals with long COVID. Cognitive rehabilitation, counseling, and mental health support from psychologists or psychiatrists can help manage these issues.
5. Sleep management: Sleep disturbances are common in long COVID syndrome. Strategies for improving sleep hygiene, relaxation techniques, and, in some cases, medications may be recommended to address sleep issues.
6. Nutritional support: A balanced and nutritious diet can support overall health and aid recovery. Dietary interventions may be recommended based on individual needs and symptoms.
7. Support groups and patient education: Participating in support groups or online communities with fellow long COVID patients can provide emotional support, share experiences, and offer practical tips for coping with the condition. Education about long COVID and its management is also crucial for patients and their caregivers.
8. Medications and targeted therapies: As research progresses, specific medications or targeted therapies may be developed to address the underlying mechanisms of long COVID. This could include anti-inflammatory drugs, immunomodulatory therapies [21], or medications targeting specific symptoms or organs affected by the condition [22].

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, immuno-modulatory 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.

Official health websites for the latest developments in the understanding and management of long COVID syndrome are: World Health Organization (<https://www.who.int/>), Centers for Disease Control and Prevention (<https://www.cdc.gov/coronavirus/2019-ncov/index.html>), National Institutes of Health (<https://www.nih.gov/>), European Centre for Disease Prevention and Control (<https://www.ecdc.europa.eu/>), The Lancet and Journal of the American Medical Association (JAMA).

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.

References

1. Crook H, Raza S, Nowell J, Young M, Edison P. Long COVID-mechanisms, risk factors, and management. *BMJ*. 2021;374:n1648.
2. Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet*. 2022;400:452-61.
3. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. *Brain Behav Immun*. 2022; 101:93-135.
4. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nat Med*. 2022;28:1461-7.
5. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019.
6. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21:133-46.
7. Soh HS, Cho B. Long COVID-19 and health-related quality of life of mild cases in Korea: 3-months follow-up of a single community treatment center. *J Korean Med Sci*. 2022;37:e326.
8. Swank Z, Senussi Y, Manickas-Hill Z, Yu XG, Li JZ, Alter G, Walt DR. Persistent circulating severe acute respiratory syndrome coronavirus 2 spike is associated with post-acute coronavirus disease 2019 sequelae. *Clin Infect Dis*. 2023;76:e487-e90.
9. Glynn P, Tahmasebi N, Gant V, Gupta R. Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines. *J Investig Med*. 2022;70:61-7.
10. Arthur JM, Forrest JC, Boehme KW, Kennedy JL, Owens S, Herzog C, et al. Development of ACE2 autoantibodies after SARS-CoV-2 infection. *PLoS One*. 2021;16:e0257016.
11. Haffke M, Freitag H, Rudolf G, Seifert M, Doehner W, Scherbakov N, et al. Endothelial dysfunction and altered endothelial biomarkers in patients with post-COVID-19 syndrome and chronic fatigue syndrome (ME/CFS). *J Transl Med*. 2022;20:138.
12. Osiaevi I, Schulze A, Evers G, Harmening K, Vink H, Kümpers P, et al. Persistent capillary rarefaction in long COVID syndrome. *Angiogenesis*. 2023;26:53-61.
13. Liu Q, Mak JWY, Su Q, Yeoh YK, Lui GC, Ng SSS, et al. Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. *Gut*. 2022;71:544-52.
14. Dennis A, Cuthbertson DJ, Wootton D, Crooks M, Gabbay M, Eichert N, et al. Multi-organ impairment and long COVID: a 1-year prospective, longitudinal cohort study. *medRxiv*. 2022; DOI: 10.1101/2022.03.18.22272607.
15. Spudich S, Nath A. Nervous system consequences of COVID-19. *Science*. 2022;375:267-9.
16. Peluso MJ, Deveau T-M, Munter SE, Ryder D, Buck A, Beck-Engeser G, et al. Impact of pre-existing chronic viral infection and reactivation on the development of long COVID. *medRxiv*. 2022; DOI: 10.1101/2022.06.21.22276660.
17. Zubchenko S, Kril I, Nadizhko O, Matsyura O, Chopyak V. Herpesvirus infections and post-COVID-19 manifestations: a pilot observational study. *Rheumatol Int*. 2022;42:1523-30.
18. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185:881-95.e20.
19. Choi TG, Kim JY, Kunutsor SK, Jae SY. The emerging role of exercise and optimal exercise prescription for improving the symptoms of long COVID. *Korean J Sports Med*. 2023;41:119-29.
20. Pifarré San Agustín F, Roselló i Aubach L, Hilenó González R, Palmi Guerrero J, Bañeres L, Planas i Anzano A, Prat Subirana JA. The use of oxygen as a possible screening biomarker for the diagnosis of chronic fatigue. *Apunt Sports Med*. 2022;57:100379.
21. Pitt B, Tate AM, Gluck D, Rosenson RS, Goonewardena SN. Repurposing low-dose naltrexone for the prevention and treatment of immunothrombosis in COVID-19. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:402-5.
22. Zhang L, Xu Z, Mak JWY, Chow KM, Lui G, Li TCM, et al. Gut microbiota-derived synbiotic formula (SIM01) as a novel adjuvant therapy for COVID-19: an open-label pilot study. *J Gastroenterol Hepatol*. 2022;37:823-31.