



Long-Covid and Pain: Pathophysiology and Management

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Abstract

Purpose of Review Since its origin on December 12, 2019, SARS-CoV-2 has shaken the globe, and while pandemic restrictions have lifted, many individuals who survived the acute viral infection continue to suffer chronically from complications for months and even years.

Recent Findings The physiologic, multi-organ complications related to this viral infection can be severe. The ongoing symptoms of SAR-CoV-2 extending beyond 4 weeks are referred to as Long-Covid, with the most common complaints being related to pain. As the pathophysiology continues to be investigated, the current hypothesis is that the angiotensin-converting enzyme 2 (ACE2) receptor plays a major role in the spread of the virus throughout multiple organ systems leading to pain, inflammation, fibrosis, and vasoconstriction. Currently, there is limited research regarding the pathophysiology of Long-Covid and why there is such variability amongst patients in regard to severity, duration, and organ system involvement.

Summary This review attempts to outline the current understanding of Long-Covid pathophysiology and summarizes management strategies, particularly pain control, for those currently affected by its symptoms and their treating providers.

Keywords Long-Covid · Pain management · Chronic pain in Long-Covid

Introduction

While the pandemic may have ended, SARS-CoV-2 (Covid-19) has resulted in effects that we are still in our infancy of understanding. As of July 5, 2023, there have

been over 767 million confirmed cases of Covid-19 and 6.9 million deaths [1]. While the majority of individuals will only experience mild to moderately severe symptoms, an estimated 31–69% of survivors are at risk of developing physiological and multi-organ complications [2, 3]. Initially as the terminology was confusing and lacked a consensus definition, the National Institute for Health and Care Excellence (NICE) attempted to establish the definition based on the duration of the illness. Long-Covid encompasses ongoing symptomatic Covid-19 lasting anywhere between 4 and 12 weeks after initial infection, in the absence of a different diagnosis. Alternatively, the National Institute of Health (NIH) denoted Long-Covid as the persistent symptoms experienced beyond 4 weeks [4]. Over 50 symptoms of Long-Covid have been documented, including fatigue, myalgia, arthralgia, palpitations, chest pain, cognitive impairment, dyspnea, and anxiety [5, 6]. This review summarizes and examines the current understanding of the pathophysiology of Long-Covid, more specifically in its relation to pain (myalgia, arthritis, and peripheral neuropathy) and the management and treatment guidelines for pain control.

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Pathophysiology

Various studies have shown that the most common complaint related to Long-Covid is pain, through either the involvement of the central or peripheral nervous systems. These complaints vary from musculoskeletal complaints of myalgia, arthralgias, and arthritis to peripheral neuropathy, atrophy, and muscle dysfunction [7].

The mechanism for the persistent symptoms after the acute phase of the disease continues to be an area of debate. Since the early days after this entity was recognized, it was linked to potential sequela of organ damage, the different rates of recovery for each organ system, chronic inflammation, sequela of critical illness, post-intensive care syndrome, or even sequela from medication management during the acute phase [8]. These multiple and potentially overlapping etiologies could explain the hundreds of biomedical findings that have been documented and patients' reporting dozens of symptoms at times, across multiple organ systems [9]. More recent studies suggest a closer association between the mechanism of the acute phase and the development of Long-Covid.

During the acute phase, SARS-CoV-2 virus enters cells via the angiotensin-converting enzyme 2 (ACE2) receptor where it replicates and activates an inflammatory response leading to the infiltration of immune cells and various cytokines [10, 11]. The ACE2 receptor is expressed in many tissues, suggesting its involvement in Long-Covid. This overexpression of the ACE2 receptor leads to the increased spread of the virus through the vascular system. The production of chemical mediators via M1 macrophages in addition to viral endocytosis reduces ACE2 receptor density causing an increase in angiotensin II levels, thus increasing the inflammation, fibrosis, and vasoconstriction throughout the body [12]. Studies have shown that this process activates a positive feedback loop producing more ACE2 receptors, stimulating the increase in levels of angiotensin II.

In examining lung damage, SARS-CoV-2 has been shown to interact with Toll-like receptors (TLRs), increasing the expression of myeloid differentiation gene 88 (MyD88) which activates nuclear factor kappa B (NF- κ B) and promotes the inflammatory cascade [13]. The activation of NF- κ B extends beyond just damage to the lungs, as high levels can stimulate cytokines (IL-1, IL-2, IL-6, TNF- α), cell adhesion proteins (ICAM, V-CAM), chemokines (IL-8), and inducible enzymes (nitric oxide synthase and cyclooxygenase II), amplifying the hyper-inflammation effect and oxidative stress [14].

Central Nervous System Involvement

The presence of SARS-CoV-2 mRNA remaining in the central nervous system post-acute phase appears to contribute to neuronal loss. It has been suggested that the presence of mRNA

triggers neuroinflammation through activation of microglia and mitochondrial failure. The induced systemic autoimmune reaction and local microthromboses could also contribute to persistent neuroinflammation [15–21]. This persistent inflammation causes endotheliitis, which disrupts the blood-brain barrier [22]. Two studies focusing on brain MRI findings in symptomatic Covid-19 patients highlighted structural alterations in several regions of the brain [23, 24].

These studies hypothesize that mast cell activation syndrome (MCAS) could lead to Long-Covid. Another study suggests that the virus induces a cytokine storm [25]. Higher levels of NLRP3 gene have been seen in Covid-19 patients. NLRP3 in increased amounts can cause a pathological accumulation of fibrillar amyloid- β leading to neurodegenerative diseases, and when in combination with interleukin-1 β and interleukin-18, it negatively alters cerebral and neuronal function [26].

The activation of inflammatory response from the aforementioned mechanism resulting in autonomic dysfunction, specifically disproportionate sympathetic activity, has been found in patients with chronic pain due to Long-Covid. This sympathetic activation then damages the cardiovascular, respiratory, renal, gastrointestinal, musculoskeletal, and immune systems [9, 27].

Post-Covid headache symptoms are attributed to this cytokine storm and the immunomodulation of the glial and trigeminal-vascular system [28].

Musculoskeletal System

The expression and production of myokines (muscle-derived cytokines) signal the normal physiologic inflammatory response after exercise and are amplified in the presence of SARS-CoV-2 [29]. Myokines cause stimulation of the ACE2 receptor that is overexpressed after viral invasion of the peripheral nervous system (PNS) [29, 30]. Normally, activation of myokines inhibits M1 macrophages which are pro-inflammatory and increases the number of M2 macrophages (anti-inflammatory); however, after SARS-CoV2 infections, the opposite effect occurs: a decrease of M2 with an increase of M1 activating TLRs, TNF- α IL-1, and other pro-inflammatory markers, resulting in myalgia, arthritis, neuronal demyelination, myofibril atrophy, and necrosis [29, 30]. Unfortunately, the exact mechanism of the musculoskeletal infection and why it more strongly impacts certain individuals is not fully understood and requires further study.

Management Strategies

Given the evolving understanding of the pathophysiology of Long-Covid, effective treatment protocols continue to be explored. The current recommendation is to tailor treatment

individually, based on presentation. A multi-modal, multidisciplinary approach to care for Long-Covid has been advocated given the myriad of presentations. Long-Covid is currently hypothesized to be secondary to hyperinflammation and oxidative stress; if true, starting pharmacological options should include non-steroid anti-inflammatory drugs (NSAIDs), antioxidants, and corticosteroids [19, 31]. Another important aspect of management includes the role of physical therapy. Since physical therapy is a current recommendation for anyone with chronic pain who is able to participate, this referral should be considered. Physical therapy has been shown to reduce the severity of symptoms while also strengthening affected muscles and joints, improving stamina, and reducing disability [32]. Other options needing further study include the use of muscle relaxers, magnesium, and neuropathic pain medications such as gabapentin or pregabalin.

Headache is one of the most common debilitating pain symptoms of Long-Covid. It can present as a new headache or a worsening of a preexisting headache. Symptoms most often resemble tension-type or migraine headaches, with or without an aura. Signs of sympathetic dysfunction are also commonly seen. Treatment modalities include both pharmacological and non-pharmacological options. Pharmacologically, NSAIDs, and acetaminophen are the first-line treatments. Low-dose antidepressants and onabotulinumtoxinA (BTX) have been recommended. The use of integrative medicine and behavioral health modification also has been suggested [27]. Stellate ganglion blocks have been studied to address symptoms of dysautonomia such as fatigue, labile blood pressure, and heart rate variability that can develop with Long-Covid [33, 34].

Discussion

The acute phase of SARS-CoV-2 has been shown to have a multisystem impact, involving ACE2 receptors which are expressed in many tissues and organs. We cannot identify the pathophysiology and conversion to Long-Covid in the post-acute phase, why it affects certain individuals more severely than others, or why individuals manifest such a wide variety of symptoms. There is a current lack of quantitative strength in reliable data to explain these findings. Additionally, there is a lack of generalized consensus on the timeline and definition of Long-Covid. One paper documented over 50 different symptoms of Long-Covid. Finally, asymptomatic infected individuals are very hard to identify and likely would be missed by these studies. There was also great variability in inclusion criteria in many of these studies, and they cannot be compared equally. Some studies had very small sample sizes or used healthy volunteers as a control group. Because of the lack of consensus and the ambiguity of the pathophysiology, the majority of the current recommendations

for management have resulted in little to no improvement in treatment. Future studies focusing on long-term trials and follow-up with a global sharing of data are recommended to improve developing criteria and appropriate management.

Conclusion

The SARS-CoV-2 virus has great variability in symptomatology, duration, and management. We have provided a literature review for identifying the pathophysiology of Long-Covid which we hope will lead to a better understanding of the virus that caused this global pandemic. The data available has been somewhat limited if evaluated individually, but when taken together may paint a more comprehensive picture of the disease course and facilitate better management in the future. Only with better understanding of this infection will we be able to properly identify treatment protocols for managing the variety of symptoms long term.

Author Contribution Richard Rice, MD Primary author of the body of the manuscript. Breanna Lauinger, MD Primary author of the abstract portion of the manuscript, secondary editor of the manuscript. SriKrishna Chandran, MD Secondary editor of the manuscript; checked reference accuracy. Arif Valliani Secondary editor of the manuscript; added a reference to the reference list with appropriate citation. Luis Escano Volquez, MD Secondary editor of the manuscript; added two additional references with appropriate citations to the body of the manuscript. Corresponding author: Sarah Money, MD Primary investigator for the manuscript; secondary editor of the manuscript.

Data Availability Not applicable.

Declarations

Ethical Approval No ethical board reviews were performed for this literature review.

Conflict of Interest The authors declare no competing interests.

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