



Post-COVID Pain Syndromes

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Accepted: 18 February 2022 / Published online: 10 March 2022

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Abstract

Although the number of SARS-CoV-2 new cases may be declining due to the implementation of the vaccine in the USA, there is a rising cohort of people with long-term effects from the virus. These long-term effects include loss of taste, heart palpitations, and chronic pain syndromes. In this commentary, we assess the current literature to appraise the knowledge of long-term COVID-19 effects related to long-term pain syndromes including testicular pain, headache, chronic pain, and chest pain.

Keywords post covid headache · post covid testicular pain · post covid syndrome · post covid chronic pain

Introduction

Emergent in human populations in 2019, the coronavirus disease (often referred to as COVID-19) is a respiratory condition caused by the viral agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. As of November 28th, 2021, the World Health Organization has documented more than 259,000,000 global cases and 5,000,000 global deaths [2]. More recently, the number of COVID-19 cases has been decreasing as the vaccine is being distributed largely. Although the amount of new cases is decreasing with the large-scale implementation of the COVID-19 vaccine, many long-term side-effects of the virus are affecting the people who have previously contracted the virus. Investigation of post-acute complications of coronavirus disease remains an emerging field. A meta-analysis by Lopez-Leon et al., conducted in January 2021, found that 80% of patients who have recovered from COVID-19 report at least 1 long-term symptom, defined as an effect beyond 2 weeks following acute infection [3]. While the most common reported post-COVID manifestations are fatigue, headache, attention disorder, hair loss, and dyspnea, the CDC reports a long list of potential post-COVID symptoms including loss of smell or taste, dizziness, heart palpitations, chest pain, myalgias, depression, anxiety, and fever [3, 4]. Furthermore,

there have been numerous documented accounts of atypical post-COVID symptoms that justify additional investigation. There have also been numerous published findings of atypical chronic pain associated with SARS-CoV-2 infection, particularly in patients who were admitted during part of their course of care.

A literature search was performed to identify research articles related to development of various kinds of chronic pain following a COVID-19 infection.

PubMed and Google Scholar were used to search the terms (post covid headache) OR (post covid testicular pain) OR (post covid syndrome) OR (post covid chronic pain). Filters were applied to include clinical trials, meta-analyses, systematic reviews, randomized controlled trials, and only articles published within the past 2 years. Papers were additionally appraised by two reviewers based on availability of full text articles and the discussion of specific patient cases and symptoms documented outside of a hospital context. There were no disagreements, and no relevant articles were excluded. A total of 30 articles were discussed in this commentary.

Given the limited available literature on long-term, post-infection symptoms in SARS-CoV-2 patients, it is important that researchers diligently investigate all possible post-COVID symptoms and work to identify potential mechanisms of their occurrence. An increased breadth of knowledge on post-COVID complications will not only improve long-term patient outcomes but may also provide insight into interventions that can be taken during acute illness to avoid lasting impacts on patient quality of life. In this commentary, we discuss the available literature on chronic pain, long-lasting testicular pain, headache, and chest pain

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in patients following SARS-CoV-2 infection in order to assess the incidence of these cases, potential risk factors, and possible mechanisms to explain the occurrence of these phenomena.

Discussion

Long-lasting Testicular Pain

There is growing evidence that a rare long-term complication of SARS-CoV-2 infection is testicular pain. Case reports by Marca et al. and Kim et al. document instances of atypical abdominal and long-term testicular pain in patients following infection with SARS-CoV-2 [5, 6]. It has been proposed that the presence of high concentrations of angiotensin converting enzyme 2 (ACE2) in kidney and testicular tissue may help to explain the prevalence of long-term testicular pain in COVID-19 patients. SARS-CoV-2 appears to have a strong affinity for ACE2 receptors, serving as a pathway for viral entrance into human cells [6]. Given high expression of ACE2 in spermatogonia, Sertoli cells, and Leydig cells, it is possible that SARS-CoV-2 binding to ACE2 receptors in testis may induce inflammation and facilitate testicular damage and orchitis in infected patients [6, 7].

While viral interaction with ACE2 in the testicular tissue may explain the mechanism in atypical testicular pain in some cases [6, 7], it has been noted in other studies that the SARS-CoV-2 virus was not found to be present in the semen or testicular tissue [8]. A case study by Paoli et al. demonstrated that viral mRNA was not present in a patient's semen or urine that had tested positive for the virus through a nasopharyngeal swab [9]. While there was not mRNA found in the urine, semen, or testicular tissue — a study by Holtmann and colleagues found there to be a decrease in quality of sperm with a moderate COVID infection [10]. Another study from Corona et al. suggests that COVID-19-associated orchitis-like syndrome could be the result of vasculitis due to abnormalities in coagulation and segmental vascularization of the testis [7].

Given these discrepancies in findings regarding a potential mechanism for pain, it is reasonable to assume that there may be a variety of mechanisms for long-lasting testicular pain in post-COVID patients and clinicians should focus on treating symptoms and identifying patients who are at risk for these post-COVID effects. Due to the increase in COVID-19-related testicular pain as a long-term consequence, there is a need to find a proper treatment plan for these patients. Generally, to treat testicular pain, it is recommended to use ice to reduce swelling or take acetaminophen/ibuprofen; however, further study should be conducted to assess and determine the best treatment plan for

COVID-19-related testicular pain. Furthermore, risk factors should be identified for the development of testicular pain with COVID-19 to better prevent its occurrence.

At the University of Wisconsin-Madison Pain Clinic, there have been several cases of post-COVID testicular pain. These cases at UW Pain Clinics can be added to this emerging field of interest analyzing long-lasting long-term testicular pain in patients following infection with SARS-CoV-2.

Chronic Pain

Similar to long-term testicular pain, chronic pain is another atypical symptom following COVID-19 that should be investigated further. Chronic pain is of particular concern for COVID patients who have been admitted to the hospital, particularly the ICU, for their care. Investigations into risk factors for long-standing pain have identified potential risk factors and mechanisms to explain the phenomenon in patients who have been seen in a hospital setting for coronavirus disease [11]. Potential risk factors include acute pain, prolonged ventilation, prolonged immobility, neuromuscular blockade, repeating proning, and neurological insult [11]. Additionally, patient age and overall physical condition likely contribute to patient risk for chronic pain post-infection. Elderly patients and patients with more underlying disorders, particularly hypertension, have been shown to be at a greater risk for chronic pain following treatment for coronavirus [11, 12]. It has been proposed that patient weakness may contribute to rapid deconditioning and joint-related pain, which may help to explain why chronic shoulder pain has been particularly prevalent in patients who were seen in the ICU for coronavirus treatment [13].

While the exact mechanisms causing post-COVID pain in various parts of the body are unknown, a phenomenon of protracted immunosuppression, known as PICS (persistent inflammation, immunosuppression, and catabolism syndrome), has been presented as a potential major contributing factor for the presentation of post-COVID symptoms [14]. PICS facilitates inflammation, immunosuppression, and catabolism that may exacerbate or make patients more susceptible to the ACE2-mediated infiltration of testicular cells, instances of chronic pain, and other more common symptoms associated with post-COVID syndrome such as fatigue, headache, and dyspnea [14]. PICS typically occurs following an event which prompts a systemic inflammatory response. Following the acute inflammatory response and initial infection, patients experience a compensatory anti-inflammatory response [14]. It is when this compensatory response is disproportionately aggressive for the amount of initial inflammation that patients experience the phenomenon of immunosuppression, known as PICS [14, 15].

The treatment for chronic pain is extremely variable and beyond the scope of this narrative; however, the treatment

for COVID-19-related chronic pain should be assessed. Further study should determine the most efficacious way to treat COVID-19-related chronic pain and if it differs from the usual course. While it is likely that a portion of the long-term pain experienced by patients can be explained by the effects of prolonged hospitalization, including intubation and immobility, the growing evidence of post-COVID pain syndromes indicates that infection with COVID-19 may independently contribute to patients' lasting pain. Additional research should be conducted to evaluate the extent to which COVID-19 contributes to the chronic pain patients' experience, independent of other contributing factors associated with prolonged hospital admissions.

Headache

Although COVID-19 is primarily a respiratory illness, headache is an acute symptom during infection and also has been shown to be a potential long-term problem following the acute phase of the infection. A literature review from Rahman et al. found headache and dizziness to be the most common neurological manifestation in multiple studies [12, 16, 17]. To assess the neuro-invasion by a corona virus and influenza A, Lahiri and Ardil analyzed the current literature and found the general consensus to be that there is a hematogenous spread and retrograde axonal transport [18–22]. Other than this, Lahiri and Ardila also mentioned a few other potential mechanisms, such as a cytokine storm, of neuro-invasion proposed from a few other studies.

Since headaches lower a person's quality of life and depending on the severity can affect daily living activities, it is important to determine patients who are at risk for headaches long-term after contracting COVID-19 to aid in prevention of this consequence. Once a patient is experiencing COVID-19-related headache, it may be difficult to distinguish the difference between a primary headache from a secondary headache disorder when COVID-19 is a factor, so a neurologist may be needed [23]. The guidelines for management for headache in adults in the primary care setting vary based on the type of headache present in the patient; however, one of the first general practice points for the management of a primary headache in adults is to rule out secondary headache [24]. Since there are currently no official guidelines for the treatment of headaches once they are determined to be associated as a long term post-COVID-19 complication, there are many patients suffering from these long-term headaches.

One case study assessing the treatment of refractory headache in the setting of COVID-19 pneumonia found that a patient who had controlled migraines did not respond to their usual effective acute therapy [24]. The study also mentioned that anti-convulsants may offer benefits with the lowest risk of side-effects and medication interactions [24].

This case however was when the patient acutely was affected with the coronavirus. One physician, Dr. Brain Plato, was quoted saying that “for those who have persistent symptoms, probably the thing we are finding to be most effective might be to put them on a course of steroids...” and mentions there being a use of other preventative and as needed medications [25]. Other physicians online mention the potential benefit of breathing exercises. While there are many proposed modalities for the treatment of long-term headaches associated with COVID-19, there are no official guidelines for doctors to follow. It is important for there to be further research into the treatment of headaches that are long-term consequences to COVID-19 to help these patients.

Chest Pain

A major concern in patients who present with long-term pain following infection with SARS-CoV-2 is chest pain, as there is evidence to suggest that persistent cardiac symptoms like chest pain, palpitations, and tachycardia for up to 6 months indicate underlying cardiac sequelae [26]. Previous radiologic investigation of patients who recovered from coronavirus found persistent cardiac abnormalities in 78% of patients and myocardial inflammation in 60% of patients [27]. This investigation also found no association between the incidence of cardiac sequela and severity of acute coronavirus illness [27]. A separate investigation of athletes who recovered from COVID-19 found similar instances of myocardial inflammation in 46% of patients, providing additional evidence for both the risk of long-term cardiac sequela and the independence of cardiac damage from illness severity and overall patient health [28]. While not all instances of post-COVID chest pain may be indicative of underlying cardiac abnormalities, it is important for clinicians to investigate all instances of post-COVID chest pain as it is both a prevalent and potentially concerning finding for patient cardiac health.

Persistent chest pain is one of the most common long-term symptoms in patients who have recovered from SARS-CoV-2. A clinical follow-up of 130 patients recovering from SARS-CoV-2 found that 13% of patients reported persistent chest pain at least 60 days after initial infection [29]. Additionally, a separate, retrospective study of 274 patients in Nigeria noted similar results, finding that 10% of patients enrolled in the study self-reported symptoms of chest pain following coronavirus infection [30]. There are a variety of proposed mechanisms for post-COVID chest pain, each of which should be investigated by clinicians in patients presenting with correlated symptoms. Chest pain may be secondary to cardiac damage, as previously discussed. The ACE2 receptor, which SARS-CoV-2 displays a high affinity for, is highly expressed in myocardial cells, which offers a possible route of entry for the virus to cause long-term cardiac damage [31]. ACE2 receptors are also highly expressed

in type II alveolar epithelial cells, which accounts for the lungs being the primary target of SARS-CoV-2 infection [31]. Underlying pulmonary embolism has also been proposed as a potential mechanism for post-COVID chest pain, particularly when accompanied by shortness of breath in patients [32]. Patients who present with long-term chest pain following coronavirus infection should be thoroughly investigated for pulmonary emboli, as this could present a life-threatening complication in high-risk patients. While post-COVID chest pain can be acutely managed with pain medication, it is critical for clinicians to investigate these patients for pulmonary emboli as well as underlying cardiac conditions such as pericarditis, myocarditis, and other cardiac abnormalities.

Summary

COVID-19 has taken the world by storm and there is a growing body of literature on how it can acutely manifest in patients. Now that COVID-19 has been affecting patients for approximately 2 years, we are discovering the potential long-term effects possible after contracting the virus. There appears to be an increase in the number of cases of long-term headaches, chest pain, testicular pain, and chronic pain being reported after COVID-19 infection. It has been postulated that secondary to the COVID-19 pandemic, chronic pain may be expected to rise in both the immediate and long-term [33]. Further analysis of the literature should be conducted in the future to continue to analyze the chronic effects of COVID-19.

Author Contribution Kenneth J Fiala: contributed to the literature review and manuscript writing. Joshua M Martens: contributed to the literature review and manuscript writing. Alaa Abd-Elsayed, MD, MPH: contributed to the literature review and manuscript writing.

Declarations

Conflict of Interest Dr. Alaa Abd-Elsayed receives consulting fees from Medtronic and Avanos.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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