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Review

COVID-19 and Pain

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ABSTRACT

SARS-CoV-2 causes COVID-19, which includes acute respiratory tract infections with a variety of manifestations such as pneumonia and bronchiolitis which are accompanied by other symptoms such as wheezing, cough, respiratory distress, and pain. The novel Coronavirus has caused millions of deaths and increasing challenges for healthcare professionals globally. When the virus enters our organism through nasal mucosa it is identified by the innate immune system such as macrophages and mast cells, therefore producing pro-inflammatory cytokines including IL-1β, IL-6, and TNF. The production of cytokines mediates fever, malaise, depression, anxiety, loss of appetite, hyperalgesia, and pain. Here in this paper, we report the interrelationship between COVID-19 and pain.

Keywords: *COVID-19; SARS-CoV-2; Inflammation; Cytokine; IL-1β; IL-6; TNF; Immune;Pain*

INTRODUCTION

In December of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surfaced in the city of Wuhan, China, causing the coronavirus disease (COVID-19) which then spread quickly and became a global pandemic (1). On January 30th, 2020, The World Health Organization declared the COVID-19 outbreak to be an International Public Health Emergency (2). As of January 24th, 2021, there have been over 98 million confirmed cases of Covid-19 globally and it has led to more than 2 million deaths (3). The pandemic has had a great impact on society, the economy, and has presented challenges for healthcare professionals globally.

The virus is highly transmissible in humans, by droplets, through speaking, sneezing, and coughing, in close parameters, or by surface contact (4). SARS-CoV-2 causes acute respiratory tract infections and older individuals and those with a weakened immune system and comorbidity are at higher risk for experiencing severe complications. Symptoms of COVID-19 can range from mild to severe and include shortness of breath, dry cough, fatigue, fever, pneumonia, respiratory failure, systemic inflammation, and pain (5).

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COVID-19 can cause acute and chronic pain, with the latter becoming increasingly apparent as a long-term symptom. For this, coping with residual pain is an important aspect of treatment, to improve the quality of life for patients. Pain accompanying COVID-19 is linked to inflammation and the "cytokine storm", with the rapid release of pro-inflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF), and this article aims to explore this relationship between COVID-19 and pain.

SARS-CoV-2 and the Innate Immune System

SARS-CoV-2 enters the body through nasal mucosa, where it replicates and infects the nasal cavity (6). It can continue to replicate down the respiratory tract, from the throat, to bronchia, and into the lungs, causing severe COVID-19, and potential brain infiltration and death (6). A prompt innate immune response to SARS-CoV-2 can lead to virus clearance and immune memory. An immediate and active immune response can contain and clear the virus, while a delayed response and increased inflammation can lead to serious complications, such as pneumonia, and death (4). Those with a weakened or compromised immune system are at higher risk for severe disease.

Upon entry, the virus is recognized by the innate immune system including mast cells (MCs) and macrophages. MCs are innate immune cells that are ubiquitous in the body, which are highly heterogeneous and function differentially in response to diverse stimuli (7). After activation, MCs release histamine, proteases, and proinflammatory cytokines and chemokines. This can be protective and help to clear infection, but an overactive response with proinflammatory mediators can be damaging, exacerbating inflammation, and leading to severe disease.

Macrophages are innate immune cells which intervene immediately when the microorganism enters the body. SARS-CoV-2 activates macrophages through Toll-like receptors (TLRs), and they produce pro-inflammatory cytokines which aggravate COVID-19 and generate pain.

COVID-19 infection can cause an exaggerated inflammatory response deemed the "cytokine storm". In response to SARS-CoV-2 entry, macrophages and MCs initiate signaling cascades and activate transcription factors, which induce pro-inflammatory cytokines including IL-1, IL-2R, IL-6, IFN-y, IP-10, MCP-1 and TNF (8) (5). A sudden increase in these pro-inflammatory cytokines, and the subsequent convergence of macrophages, neutrophils, and T cells to the infection site, creates the "cytokine storm", which can lead to tissue and vascular damage, organ failure, lung injury, and death (9).

Evidence proposes the "cytokine storm" is involved in patients with severe COVID-19 and is a common cause of mortality and complications, with studies finding significantly heightened levels of IL-1β, IL-6, and TNF in living and deceased patients (5) (10) (11).

COVID-19 Pain

COVID-19 is often accompanied by pain, with the most frequently reported pain symptoms including headache, widespread myalgia, and back and neck pain. In fact, myalgia and headache are often the first symptoms experienced by patients. Inflammation plays a vital role in the development of pain.

Muscle pain has been reported to affect 21-36% of patients (12) (13) and is associated with inflammation. The release of pro-inflammatory cytokines during "the cytokine storm" can activate the formation of pain mediator prostaglandin E2 (PGE2), which is induced by IL-1β on macrophages.

COVID-19 induced headache operates by similar mechanisms as migraines and common headaches. Inflammation causes nociceptive sensory neurons to become activated in response to cytokines. Other possible causes could include viral neuroinvasion, hypoxia, or thrombosis.

COVID-19 not only produces classic respiratory virus symptoms, but a growing amount of evidence continues to show neurological symptoms such as headache, anosmia (loss of smell), ageusia (loss of taste), nausea, myalgia, confusion, and disorientation (14) (15) (16), as well as the development of persistent pain. Following SARS-CoV-2 infection, the rapid release of cytokines such as IL-1β, IL-6, and TNF, can mediate fever, malaise, depression, anxiety, loss of appetite, hyperalgesia, and pain.

Chronic pain is characterized by hyperalgesia, sensitivity to thermal and mechanical noxious stimuli, and allodynia, sensitivity to non-noxious stimuli. Altered neuronal plasticity can affect sensitization in the peripheral and central nervous system (CNS), heightening perceptions of pain and leading to chronic pain. Pro-inflammatory cytokines can act on pain-sensing nociceptors in the neurons of peripheral tissues and cause pain sensitivity.

COVID-19 pain occurs when SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is a protein that acts as an entry point for virus to infect cells. ACE2 receptor is present in different cells, including the epithelium of the nose, mouth, and lungs. The virus uses a "spike" surface protein to bind to ACE2 and allow it to infect the cells, resulting in an imbalance of ACE2 and lung injury (17). SARS-CoV-2 has been detected in cerebrospinal fluid and can produce neurological symptoms, and ACE2 has also been detected in neurons and microglia in mice in the spinal dorsal horn. There, ACE2 is associated with pain alleviation (18), but a reduction of ACE2, which has been used by the virus, can lead to the accumulation of Angiotensin II (Ang II) with low levels of Angiotensin-1-7, causing COVID-19 pain (17).

Cytokines in Pain

Cytokines are small, protein-based signaling molecules involved in the communication between cells in immune responses (19). They can have autocrine, paracrine, or endocrine actions, and can be pro-inflammatory or anti-inflammatory. During SARS-CoV-2 infection, activated immune cells, such as MCs and macrophages, produce pro-inflammatory cytokines including IL-1β, IL-6, and TNF. The production of these cytokines exacerbates inflammation and creates fever, destruction of tissue, pain, and may lead to shock and death (20). Overwhelming inflammation is harmful to the host and plays a central role in pain development. Some pro-inflammatory cytokines have been associated with pain amplification, with evidence showing a strong correlation with IL-1β, IL-6, and TNF.

The pro-inflammatory cytokine IL-1β has been seen to start and maintain chronic pain. IL-1β is expressed in dorsal root ganglion (DRG) neurons in response to nociceptive stimulus after CNS injury (21) (22). It has been associated with increased production of PGE2 and substance P, which can create inflammatory nociception, and injection of IL-1β has also been shown to initiate hyperalgesia (23) (24). Because of its implication in pain, IL-1β could provide future opportunities in therapy if it can be blocked.

IL-6 is active in neuropathological events, and evidence has shown that it is associated with neuropathic pain behavior. IL-6 is normally present in low levels in the brain, and a substantial increase results with neurological disorders such as Alzheimer's disease and Parkinson's disease, brain ischemia, and brain cancer. But at the same time, IL-6 is important for regeneration (25), oligodendrocyte differentiation (26), and acts as a neurotrophic factor (27). IL-6 has been seen to facilitate and exacerbate pain after nerve injury (28). In a rodent model of sciatic cryoneurolysis (SCN), a valid neuropathic pain model, IL-6 was seen to increase in the brain after SCN and cause sensitivity to noxious and non-noxious stimulus after intrathecal infusion (29). It has also been linked to nociceptor and central sensitization (30) (31).

TNF is another cytokine that is a pain mediator. It acts on different signaling pathways, regulating NF-kB and apoptotic pathways, and activates stress-activated protein kinases (SAPKs) in the brain. Its two receptors, TNFR1 and TNFR2, are found in glia cells and neurons, and TNFR1 signaling contributes to inflammation, tissue degeneration, and the development and continuation of neuropathic pain (32). Increased TNF levels are seen at sites of peripheral nerve injury (33) and endoneurial injection has been shown to initiate symptoms of pain without injury (34).

CONCLUSION

COVID-19 produces a range of symptoms, from cough, fatigue, and fever, to pneumonia, respiratory failure, systemic inflammation, and pain. The most common pain symptoms include headache, myalgia, neck pain, and back pain, and inflammation plays an important role in the development and persistence of pain. The release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF are involved in severe cases, which can lead to the "cytokine storm". These cytokines act on nociceptors in the neurons of peripheral tissues, leading to pain sensitivity. The "cytokine storm" can lead to heightened levels of pain, as well as the continuation of pain. Excessive inflammation produced by the release of proinflammatory cytokines IL-1β, IL-6, and TNF is associated with pain sensitivity. IL-1β is expressed in DRG neurons after CNS injury, activating the pain mediator PGE2, and initiating and maintaining chronic pain. After nerve injury, IL-6 can cause pain sensitivity to noxious and non-noxious stimulus and moreover, TNF signaling has been associated with inflammation and the development of pain. However, more research is necessary to expand the role that these proinflammatory cytokines, and other inflammatory compounds, play in the development and maintenance of chronic pain in COVID-19.

Conflict of interest

The authors declare that they have no conflict of interest.

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