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The global challenges of the long COVID-19

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Abstract

COVID-19 may lead to a perseverance of symptoms after recovery from the disease, a condition known as long COVID, characterized by continual cognitive, somatic and behavioral symptoms. SARS-CoV-2 infection triggers different molecular to tissue level events, given by the inherent features of each patient. The potential pathological changes which determine the array of symptoms are arduous to anticipate. There is an increasing interest to develop treatment strategies for survivors who experience a long COVID. In this respect, considering the anti-inflammatory, anti-oxidative and cytoprotective effects of melatonin (MEL) on viral infections, its potential links with COVID-19 should be researched. Several studies suggest that administration of MEL may prevent clinical deterioration and even death in patients with acute and long COVID-19. This paper briefly reviews the current status of knowledge of the pathogenic, clinical, and therapeutic features of Long COVID-19 and forthcoming directions for research and implications for the management and therapy of the disease are analyzed.

Keywords: Long COVID-19; Post COVID-19 syndrome; COVID-19; SARS-CoV-2.

Introduction

COVID-19, considered a public health emergency and then a global threat of international concern by the World Health Organization [1], is one of the most alarming diseases recently recorded [2]. Although most COVID-19 survivors recover after viral clearance, there is a percentage of patients who remain with sequelae for a variable extent of time, a condition known as Long COVID, Post-acute COVID-19 or Post COVID-19 Syndrome (PC19S) [3] which is defined as the persistence of symptoms and/or long-term complications beyond 1 month, from the onset of symptoms [4]. The U.S. Centers for Disease Control and Prevention uses the term "Post-COVID Conditions" and has designated Long COVID as "Post-acute sequelae of SARS-CoV-2 for research objectives. A definition for this term has been developed [5].

The aim of this article is to briefly reviews the pathogenic, clinical, and therapeutic features of Long COVID-19 and propose future directions for research and implications for the management and treatment of the disease.

Predisposing factors

Multiple causes have been described as predisposing factors for PC19S. Elderly, female gender, pregnancy, ethnic minority groups, poverty, smoking, high body mass index and comorbidities such as obesity, diabetes, chronic liver disease, hypertension, cardiovascular disease, and poor mental health have been linked with increased risk of PC19S [6-11].

In the most vulnerable countries, receiving a significant burden on this disease [12], it has to be considered that host immune responses associated with a viral infection can be regulated by intestinal helminths with potentially beneficial or detrimental effects [13]. According to a systematic review, preexisting geohelminth infections may impair the body's ability to fight off SARS-CoV-2 in the early phases of the infection, which could increase COVID-19 morbidity and mortality [14]. If co-infection of geohelminths and SARS-CoV-2 increases complications, then the burden of COVID-19 in endemic countries may be much worse than expected. This issue is an increasing concern in low- and middle- income countries where helminths and other infectious diseases and co-infections related to poverty are frequent [15-19].

The SARS-CoV-2 genome plays a significant role in the evolution of the illness. The mutations affect the transmissibility of the virus [20] and the possibility of developing long COVID depends on the viral strain; the incidence is higher for the Delta strain than for the Omicron strain [21]. It is plausible that the interaction of mutated viral proteins with the host cell may be altered varying the cytopathic effects. The host genome also plays a role in the progression of the disease. Some variants of the IL-6 receptor improve the outcome of COVID-19 in some patients, a phenomenon that also occurs with other proteins such as the ACE2 receptor itself. Variants of proteins such as TLR7 can lead to severe cases of COVID-19. The phenotype of each patient, given by its genotype and some environmental aspects, could be essential in the predisposition to show PC19S [22].

This paper briefly reviews the current status of knowledge of the pathogenic, clinical, and therapeutic features of Long COVID-19 and identifies those aspects in which further research is needed.

Prevalence

Long COVID is estimated to affect about 10% of recovered outpatients and 50-70% of hospitalized individuals [23]. Twenty percent of patients may show symptoms for 5 weeks or more, while 10% may be symptomatic during 12 weeks or more [24,25]. Those who are most at risk to PC19S are patients with severe acute disease who experienced CNS affectation [26]. More than 60 % of the survivors experienced PC19S [3] that may be an emerging major sequel of COVID-19.

Prevalence of long COVID is highly variable [27]. A prospective nine-month follow-up study of 177 post-COVID-19 patients showed constant symptoms in 30% of them; the most frequent symptom was fatigue [28]. A retrospective analysis of 236,379 electronic records of COVID-19 survivors was conducted. At six-month follow-up, 57% of them had one or more symptoms [29]. Systematic studies have estimated that PC19S occurs in 43% to 80% of patients that develop an acute infection [30-32] and more than 50% of the survivors had at least one symptom six months later [33]. Other studies have observed persistent symptoms in 87% of the patients at two months, 96% at three months, and 76% at six months [34-36]. A recent study of more than 2,000 PC19S patients found that 5% of them recovered promptly, 91% improved gradually over a two-year period, and 4% had a durable condition [37].

Pathophysiology

The pathophysiological mechanisms of PC19S are not well understood. The effects of SARS-CoV-2 infection go beyond replication within the respiratory system, leading to a variety of extra-pulmonary manifestations [38]. The excessive cytokine production, a pro-coagulant state, and cellular damage caused by the infection may be implicated in the progress of PC19S [4]. In the elderly, the augmented pathophysiological responses to SARS-CoV-2 infection may be due to immune-senescence, inflammasome formation, telomeric erosion, oxidative damage and genomic instability [39]. The number of CD4+ T cells producing IFN-γ was low in hospitalized aged patients and CD8+ T-cell responses were lower in patients with long COVID [40].

The cytopathic effects of SARS-CoV-2 at the cellular level in the respiratory system contribute to the development of PC19S [39]. Epithelium basal cells, which enable the lung to restore damage caused by virus replication, exhibit migratory behavior suggesting their role in respiratory epithelial repair. The regenerative capacity is often unregulated and could lead to the appearance of respiratory symptoms in PC19S patients [41,42]. These disorders have been linked to iron metabolism alterations, and patients with pulmonary sequelae usually have metabolic deregulations associated with pulmonary repair and fibrosis [43].

Brain blood vessels may exhibit structural modifications in some COVID-19 patients due to inflammatory activation of their permeability by direct viral effect. Experimentally, SARS-CoV-2 can induce neuronal apoptosis, mainly in the gyrus of the hippocampus, through Caspase-3 [44]. Bacterial meningitis affecting the hippocampus can produce apoptosis, and learning limitations often develop in survivors [45]. Thus, it is plausible that the memory and cognitive impairments in PC19S patients are consequences of the severity of cytopathic effect in the hippocampus which is crucial in memory development. Some of the cytokines produced by SARS-CoV-2 in other tissues can trigger astrocytes and microglia, which produce neural cytokines and contribute to the evolution of neuroinflammation and the alteration of GABAergic transmissions in some COVID-19 patients and cooperate to their chronic fatigue [46,47].

COVID-19 evolution has been associated with the microbiome [48]. The amount of some bacteria and fungi, primarily opportunistic pathogens, was decreased in recovered patients, while the butyrate-producing microbes were increased; these findings persisted for some organisms at 1 year after improvement [49]. Other potential factors that could affect the disease progress comprise immune system deregulation [50,51], with or without reactivation of latent pathogens such as herpesvirus 6 and Epstein-Barr virus [52,53]; immune system dysfunction [54]; autoimmunity [55,56]; endothelial dysfunction with microvascular blood clotting [57,58]; and dysfunctional signaling in the brainstem or vagus nerve [54,59].

Symptomatology

Long COVID displays a broad range of clinical manifestations, from asymptomatic individuals to those who develop critical illness that may conclusively prove fatal. This disease has more than 200 symptoms and different levels of severity, making it difficult to define [23,58]. Acute COVID-19 symptoms may persist or new onset symptoms may appear after the recovery from disease [60]. Patients with PC19S have been reported to show persistent symptoms and a poor quality of life. Contrary to the symptoms and complications of acute COVID-19 that are well established, the sequelae induced by the PC19S need more studies [61].

The main respiratory symptoms are dyspnea, cough and constant need for oxygen [4,35,47]. Pulmonary fibrosis has been pointed out as a potential long-term complication, and it has been considered that vascular disarrays may be responsible for long-term respiratory symptoms [43].

Among other long COVID symptoms, the most common include fatigue, headache, myalgia, decreased sense of smell and taste, malaise, apathy and anxiety. Cognitive dysfunction, memory impairment, poor focus, attention disorder, increased word-finding latency, difficulty in tracking complex information,

and reduced ability for multi-tasking have also been reported. The term "brain fog" is used for this symptomatology which has become peculiar of PC19S [24,29,34]. A study showed higher levels of depression, anhedonia, inattention and executive dysfunction in PC19S patients, especially in those who were 1 to 4 months post-acute phase [62]. Significant and long-lasting neurological manifestations have been reported [63,64]. It has been suggested that 80% of patients who sustained COVID-19 will show one or more neurological symptoms that can last months after the acute infection. Neurologic and cognitive symptoms tend to occur late and persist longer than gastrointestinal and respiratory symptoms [34,65]. Neurological symptoms are most frequent in young adults, while encephalopathy is more common in older adults [63].

Several organs can also become directly infected and may show long-term alterations, contributing to the symptomatology of long COVID [47]. However, the respiratory and nervous systems appear to be the most affected in terms of persistent sequels. Different clinical phenotypes may be related to distinct underlying pathophysiologic mechanisms of disease [66,67].

Adverse consequences due to multiple diseases have been documented including type 2 diabetes; thrombotic, cardiovascular and cerebrovascular diseases; encephalomyelitis and postural orthostatic tachycardia syndrome [26,34]. Recently, severe PC19S was associated with radiological evidence of myocarditis. Mechanisms explaining this correlation remain unclear [68]. Different long-term gastrointestinal manifestations have also been reported, such as dyspepsia, gastro-esophageal reflux, peptic ulcer, intestinal disorders, hepatic and biliary disease and acute pancreatitis [64].

Long detection of SARS-CoV-2 in tissues has been documented [69] in immune-compromised patients reaching up to more than a year post-infection [69-72]. Some studies have hypothesized that hidden virus in certain organs could contribute to the maintenance of certain symptoms [43].

Treatment

To date, most of the focus in identifying drugs has been placed on preventing or mitigating acute COVID-19. However, recent increasing attention has been cast on treatment strategies for post-COVID-19 patients who experience somatic, behavioral and cognitive symptoms. In this regard, nirmatrelvir and molnupiravir treatments reduced the risk of long COVID progression [73,74]. Since the main serious persistent symptoms highlighted after the infection are sleep disturbance, fatigue, anxiety, depression and mental impairment [26,61], one could speculate that melatonin (MEL) disturbance is a potential factor contributing to the long-term consequences of COVID-19 [75]. MEL supplementation may improve sleep efficiency, mood status, cognitive performance, mental health and cardiovascular disorders [26]. The therapeutic benefit of MEL in bacterial, fungal, parasitic, and viral infections have been demonstrated [76-80]. MEL is known to attenuate the COVID-19 infection through its anti-inflammatory, antioxidant and immune-enhancing properties; its use to combat COVID-19 is increasingly recommended [81-85]. The findings suggest that it is an excellent therapeutic candidate for PC19S and deserves investigation.

Prevention

Vaccination against SARS-CoV-2 decreases the risk of long COVID-19 [83]. However, reinfection of patients with different SARS-CoV-2 variants and the impact of vaccines in preventing long COVID-19 remain unknown and need further research. In this respect, MEL enhances the immune response to vaccines by increasing peripheral blood CD4+ T cells and IgG-expressing B cells [83,85,86]. Vaccine efficacy is considered inferior for high-risk population groups compared to healthy people and MEL is effective in counteracting the immunosuppression observed in aging [85]. MEL may boost the vaccine's effectiveness in healthy and immune-compromised patients and could prevent the adverse effects of the vaccine due to its antioxidant and immune-regulatory properties [83-86].

Conclusion

Long COVID-19 must be considered a major public health problem which is expected to inflict a global dramatic public health. A better understanding of this syndrome will help to unravel its pathogenesis and to develop an effective treatment; clinical trials with different drugs are required to assess their efficacy.

Comprehensive research on the long-term evolution and impact of the PC19S, reinfection with different SARS-CoV2 variants and the impact of vaccination in preventing long COVID-19 are needed. We must be ready for the potential long COVID-19 consequences and to provide health care to the people affected.

In our opinion, there is strong evidence for initiating prospective controlled trials to better characterize the effectiveness of MEL in mitigating clinical deterioration following acute COVID-19. It is a perfect candidate as an alternative or adjuvant treatment in the disease since MEL is the best natural antioxidant-anti-inflammatory-immunomodulator-cytoprotector [81-85]. In addition, evidence exists that suggest its potential direct effect on SARS-Co-2 [83].

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