



The Mini Review of The Impacts of Long COVID-19 on Multi-System

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Abstract

COVID-19 is a highly contagious respiratory illness caused by the novel coronavirus SARS-CoV-2. Symptoms of COVID-19 can range from mild to severe and include fever, cough, and difficulty breathing. As research deepens, more and more data indicate that the number of patients continue to experience symptoms of COVID-19 long after they have recovered from the initial illness. We summarized the long COVID-19 symptoms in an integrated way and found that the symptoms of each system are correlated to some extent, suggesting that a multi-system evaluation is necessary when treating COVID-19, rather than merely focusing on treating individual systems. As the novel coronavirus is a new virus and the human immune system's response mechanisms are not yet fully understood, the impact of long COVID-19 may last for a significant period of time. This review may help clinical practitioners gain a comprehensive understanding of long COVID-19 to alleviate patients' affection.

Introduction

COVID-19 is a contagious disease caused by the novel coronavirus, resulting in a global pandemic with more than 242 million cases reported in over 200 countries [1]. Transmission occurs through contact with an infected person or their respiratory droplets, with symptoms including fever, dry cough, fatigue and shortness of breath [2]. Some patients after SARS-CoV-2 infection experienced a series of ongoing symptoms over 2 months and cannot be explained by other diagnoses. Symptoms of long COVID can include fatigue, shortness of breath, chest pain, anosmia (loss of smell), and headaches, but the specific manifestations vary from person to person. In addition, some studies have shown that symptoms often manifested in the nervous system include anxiety and insomnia [3], the symptoms in the respiratory system often exhibited cough, chest tightness, chest pain [4], there are also a lot of digestive system manifestations such as loss of appetite, nausea, vomiting [5]; some patients present muscle pain, nocturia, and arrhythmia [6].

In Europe and United States a large number of people have suffered from the "Long Covid". Moreover, especially severe. But at present, the specific symptoms and related mechanisms of "Long Covid" are relatively incomplete, and the current social and medical level needs a complete "Long Covid" about 16 million Americans between the ages of 18 and 65 said they had "Long Covid" symptoms. So long COVID-19 has

had a profound effect on the world, and its impact on the global economy has been severe. European Society for Immunodeficiencies (ESID) integrated report to prepare for the prognosis of patients.

In this review, we summarized and analyzed previous researches, consulted the corresponding sequelae of the relevant systems, and summarized the common "long-term COVID-19" symptoms and corresponding brief pathogenesis, which can provide some reference suggestions to better understand the long-term effects of the virus on the body.

Effects on respiratory system

The upper and lower respiratory tracts are the main parts of the body where SARS-CoV-2 invades, and causing COVID-19 pneumonia is the most common manifestation. The novel coronavirus SARS-CoV-2 is highly contagious, and the respiratory tract acts as an interface between the internal and external environment, which is probably the most hurt and vulnerable [7]. During the infection, The SARS-CoV-2 is high affinity for ACE II (angiotensin converting enzyme 2) and ACE damage activates the host to produce pro-inflammatory and profibrotic responses which may develop symptoms of intraalveolar thrombosis and pulmonary fibrosis. Given the potential risk of SARS-CoV-2 inducing airway inflammatory and pulmonary fibrosis, early intervention treatment for COVID-19 is necessary to prevent chronic impairment of lung function due to the acute lung injury [8].

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Effects on nervous system

After COVID-19 infection, some patients have only one symptom, and some patients have multiple symptoms. 46.2% of patients had symptoms of intracranial infection, such as dizziness, headache and disturbance of consciousness. 41% of patients had cerebrovascular disease, such as apoplexy. 20.4% of patients had neuromuscular diseases, such as peripheral neuropathy, muscular atrophy, myasthenia gravis and Guillain-Barre Syndrome. Severe patients may also be complicated with bacterial infection, which may damage the blood-brain barrier, cause meningitis or encephalitis, and may also have neurological symptoms such as decreased vision and jet vomiting.

Compared with health donors who have never been infected, after infection, the up-regulated genes that when transcribed into mRNA, it is positively regulated to promote expression are mostly related to neuroinflammation and aging pathways, while the down-regulated genes that are inhibited, reduced expression are mostly enriched in the neural cell function pathway, and the expression level of genes related to the amyloid precursor protein processing pathway has no significant change, which suggests that COVID-19 infection causes the abnormal accumulation of β -amyloid protein may not be regulated by the transcription level, may eventually lead to Alzheimer's disease [9].

Patients had symptoms like hyposmia, hair loss and so on. Patients with pituitary-hypothalamic disease happened diabetes insipidus, leading to unsensitized water loss and hypernatremia. The virus passes through the circulation system or through the sieving plate to enter the CNS. Because the hypothalamus and pituitary gland express ACE2, they become the viral target.

Effects on circulation system

Sars-cov-2 can directly damage myocardial cells through angiotensin converting enzyme 2 (ACE2) receptors, after infection many patients showed circulatory system damage, moreover the abnormally activated the immune system and excessive cytokines (such as IL, IFN, TNF) caused acute and chronic myocardial injury. In addition, for patients with covid-19, there is also a risk of arterial and venous thromboembolism. The imaging findings suggest that inflammatory cardiac involvement after COVID may be a pathophysiological commonality shared among all individuals, regardless of the expression of cardiac symptoms. Inflammation may cause blood flow to slow down, thus causing arterial and venous thrombosis. (For the measures to prevent myocarditis after infection, recovered patients should avoid high-intensity exercise and pay more attention on reasonable diet.)

In addition covid-19 may cause severe hemodynamic changes and increase rhabdomyolysis and iatrogenic toxic factors which may cause the damage of renal function. From the perspective of clinical biology, viral nephropathy may lead to acute renal failure (ARF) and renal tubular dysfunction, which is characterized by impaired partial sodium excretion, sterile leukocyturia, microscopic hematuria and / or proteinuria (usually less than 400 grams per 24 hours).

Acute tubular injury plays a key role to pathological injury of kidney during COVID-19. Hemodynamic, iatrogenic or obstructive causes (through the presence of pigments in the tube) are sometimes not clearly identified. However under electron microscope, virus particles can bind to many 'normal' intracellular structures, such as polyvesicles. In addition, some studies recommended that the sars-cov-2 directly damages

the kidney endothelium, and in renal biopsy found endothelial cell injury, including congestion of glomeruli and peritubular capillaries. The existence of capillary microthrombosis around renal tubules is considered to be the main histological injury [11].

Effects on digestive system

ACE2 receptors which is the key target for SARS-CoV-2 are also abundant in the digestive system. And studies have shown that ACE2 expression in the gastrointestinal tract (such as the gastrointestinal tract, spleen, and liver especially the colon) is approximately 100 times higher than in the respiratory system[12]. So although the new coronavirus is mainly a respiratory disease, more and more data shows that the new coronavirus also has a significant impact on the digestive system. The patients may appear gastrointestinal (GI) symptoms such as anorexia, diarrhea, nausea, decreased appetite, and vomiting [13]. Research found that severe SARS-CoV-2 virus may disrupt the normal intestinal mucosa, which may lead to GI symptoms and impaired nutrient absorption. In addition, some patients may have liver dysfunction due to the cholangio cells and liver cells with high expression of ACE2 were infected and injured.

Effects on reproductive system

Covid-19 has been spreading for over three years around the world; it can not only cause respiratory system and circulatory system sequela. The virus can first through viral receptor cause host cells damage directly, moreover can trigger secondary inflammatory reactions through inflammatory cytokines [14].

During and after the infection of covid-19, the male patients sex hormone levels changed and may reduce the sperm quality. In addition, severe inflammatory damage can be detected in the testicles. Current studies revealed that the symptom severity is related to androgen expression level. In term of this, male patients have more severe reproductive symptoms than female patients. Moreover, In addition, androgen receptors (ARS) regulate the expression of TMPRSS2 (transmembrane protease serines) which is expressed in various male reproductive system, such as testis, reproductive tract, and prostate epithelial cells, which means virus can exists in semen. In addition, the expression of TMPRSS2 may be positively correlated with the severity of the disease. Since the expression of ARS in men is significantly higher than that in women, this may lead to an increased reproductive damage risk in men during COVID-19 [15,16].

Sars-cov-2 can be detected in secretion of glands and seminal vesicles, testicular and epididymal dysfunction, orchitis, decreased spermatogenesis, etc and may induce penis and erectile dysfunction. Although the levels of ACE2 and TMPRSS2 detected in reproductive organs detected are very high, among male patients with moderate to severe symptom, the incidence of orchitis and spermatogenesis disorders is still higher than expected, indicating that the virus may affect male reproductive health through another way. Since the long-term effects of COVID-19 on male infection are not clear, after recovery the patients can seek medical care for potential consequences. Future research needs to clarify the sequelae of infection, develop novel intervention to reduce the impact of sars-cov-2 on male reproductive health [17].

Effects on urinary system

Among all patients infected with sars-cov-2, the incidence of acute renal injury ranged from 0.5% to 22%. Its secondary

kidney disease may lead to serious different clinical manifestations for direct virus toxicity or immune-mediated damage [18].

In conclusion, on the basis of the current data, the kidney is likely to be the target of covid-19. Clinically, IRA and proteinuria are common and related to the histological injury of NTA (Nanoparticle Tracking Analysis). Glomerular disease can be scarce and may be related to genetic susceptibility (For example, the existence of APOL1 variant). Whether the virus exists in human renal parenchyma is still controversial. The follow-up comparative analysis of covid-19 recovered patients is crucial to determine whether sars-cov-2 causes irreversible renal damage, or whether this infection lead new-onset chronic kidney disease and renal failure (or aggravates preexisting kidney disease) [19].

Effects on endocrine system

There were no detailed statistics on the endocrine system of COVID-19. But patients experience symptoms of the endocrine system.

Exocrine pancreas was investigated in patients. In 1-2% and 17% of cases, amylase and/or lipase had improved. COVID-19 can damage β cells through direct damage, alteration of autoantigens and immune mediation. Patients with type 2 diabetes (T2DM) may have more severe insulin resistance. COVID-19 raises fetuin A, resulting in impaired insulin sensitivity. COVID-19 patients with diabetes, acute respiratory distress syndrome (ARDS) were harder to survive. Due to impaired innate immunity and downregulated ACE 2 levels in diabetic patients. The effects of COVID-19 on the endocrine system are also linked to obesity. The more fat, the more ACE 2 expression, and can act as a receptor for SARS-CoV-2.

No data related to COVID-19 and female reproductive system. However, serum testosterone was significantly decreased in male mice.

Corticosteroid insufficiency was occurred in COVID-19 patients. Patients with underlying primary adrenocortical insufficiency (PAI) were contracted lower respiratory tract infections. The hypercoagulable state in the acute phase leads to adrenal infarction. COVID-19 and hypothalamic-pituitary gland.

Patients with hyperthyroidism may develop secondary agranulocytosis [20].

Conclusion

In recent years, COVID-19 has had a significant impact on the world, hitting the world economy and the medical sector hard. After most people have had it, it's even more important to understand the after-effects of COVID-19. We summarize the sequelae that COVID-19 may cause to various systems of the human body, including the possible sequelae in the motor system, respiratory system, circulatory system, nervous system, digestive system, endocrine system, reproductive system and urinary system. In the circulatory system patients may suffer acute and chronic myocardial injury; in the nervous system, patients may suffer myalgia, dysgeusia, headache and other sequelae, and the manifestations are various; in the respiratory system, patients may suffer symptoms of pulmonary fibrosis and chronic impairment of lung function caused by acute lung injury; in the digestive system patients will experience gastrointestinal symptoms, such as anorexia, diarrhea, nausea, loss of appetite and vomiting, while the virus may damage

the normal intestinal mucosa, resulting in malabsorption of nutrients; in the endocrine system, patients may suffer symptoms such as elevated serum amylase and or lipase, decreased serum testosterone, corticosteroid insufficiency, and agranulocytosis; in the motion system, patients may experience muscle weakness in the lower extremities, and at the same time, the risk of susceptibility to Parkinson's increases; in the reproductive system, male patients may experience symptoms such as stem and erectile dysfunction, dysfunction of testis and epididymis, orchitis, and decreased sperm production may occur, female patients, however, rarely experience symptoms of this system; in the urinary system patients may develop acute renal failure and renal tubular dysfunction. Given that many systems of COVID-19 have severe or mild, long-term or short-term impacts, long-term follow-up of patients is also very necessary. At the same time, in view of the obvious impact of age on symptoms, the care of the elderly should be distinguished from young patients to a certain extent, such as setting up ventilators and medical staff for the elderly in the community, while providing adequate protective measures and ways to enhance immunity for the elderly who have not yet been infected..

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