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Analysis of COVID-19 and PASC Organ-Specific Manifestations

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Abstract: Since the first announcement of the global pandemic by WHO in December 2019, COVID-19 has become an increasing feverish topic all around the world. While many people are died or hospitalized during COVID-19 due to their severe and various manifestations, some survivors still suffering from lingering or new symptoms. This paper aims to analyze the clinical phenotypes in different organs and systems reported by patients during and after COVID-19 infection, and decline existing PASC symptoms in various body systems. In the conclusion part, some existing methods to surveillance and support the patients would be summarised and further insights would be proposed.

1. Introduction

Although lower respiratory tract infection through air-borne transmission is recognized as the main symptoms of COVID-19 at the preliminary stage, worldwide updated data delineating multiorgan involvement in patients that are infected and recovered but with new, recurring or ongoing symptoms. Many researchers have postulated that this systemic involvement is mainly correlated to the SARS-CoV-2 virus binding on angiotensin-converting enzyme 2 (ACE2) receptors located on a couple of human cells with varying densities. Coronaviruses are positive-sense, single-stranded enveloped RNA viruses with helical capsids that infect a wide range of hosts while most essential are mammals including humans, bats, etc. As the increasing amount of studies have reported, systemic multiorgan failures including gastrointestinal, cardiovascular, pulmonary, and cutaneous manifestations, are found among COVID-19 patients. On top of that, some people with COVID-19 continue to have lingering symptoms for weeks or months after they begin to recover. Experts have coined a new term for it: post-acute sequelae SARS-CoV-2 infection (PASC). Many severe and dominant symptoms in COVID-19 infection would finally lead to PASC and exert a heavy burden on the well-being of recovered patients. Herein, this manuscript aims to provide a comprehensive overview of the available literature from inception to August 12, 2021, and a proposal of future insights on multisystem involvement of the disease and PASC.

2. Gastrointestinal and Liver Involvement

Evidence of digestive system involvement in patients with COVID-19 was first reported by a group in China. Collective data demonstrated that the underlying pathophysiologic mechanism for

the digestive symptoms is related to the affinity for ACE2 receptors located in specific enterocytes in the ileum and colon in the digestive tract. ACE2 receptors are taking part in the inflammation reactions and therefore could explain the occurrence of diarrhea in infected patients. Nausea or vomiting (6%), diarrhea (9%), abdominal pain (21%), and loss of appetite (21%) were the major gastrointestinal symptoms.

One study reports a higher risk of abnormal liver chemistry including elevated ALT and AST in cases with severe COVID-19 than in those with the non-severe disease. Liver damage indices, including ALT, and AST, and total bilirubin concentrations were higher in patients with severe disease than in those with non-severe disease.

3. Anosmia and Ageusia

The transmission of virions or subviral ribonucleoprotein complexes may pass through the transcellular or a paracellular route, arriving at the olfactory bulbs of the CNS from the cribriform plate. Several tests have revealed that some people who died from COVID-19 have preferential inflammation in the olfactory bulbs. After quantifying the amount of viral RNA at autopsy, it was notable that olfactory bulbs contain the highest concentrations than other brain regions while within the parenchyma and endothelial cells, spike glycoproteins were detected. Thus olfactory bulbs may serve as the main interface for pathogens to invade. When there's a fulminant and persistent infection of the subjacent intranasal olfactory bulbs, the sterile inflammation is capable to activate microglia and astroglia, thus a rapid and robust viral clearance could be done. The specialized glia transit tubules produced by olfactory ensheathing cells (figure) may serve as the avenue for migration of cytokines, chemokines from infected olfactory epithelial tissue to the olfactory bulbs, as well as maintaining fascicles that envelope and nourish the axons of olfactory sensory neurons for the sake of efficiently conveying regenerating axons through the cribriform plate to the olfactory bulbs. One study shows the fascicles would be opened to pollutants and intranasal nose-to-brain drug delivery systems when the axon is absent. Thus, multiple channels delineate the great possibility of inflammation activation. [1]

4. Kidney Involvement in COVID-19

In the kidney, ACE2 is observed in copious cells including podocytes, epithelium of the Bowman's capsule, mesangial cells, collecting ducts and proximal cells brush border, so SARS-CoV-2 could directly infect them and cause acute tubular necrosis, mitochondrial dysfunction, the formation of collapsing glomerulopathy, protein reabsorption vacuoles, and protein leakage in Bowman's capsule. The most dominant abnormality of patients is proteinuria caused by multiple mechanisms. Some studies also reported that patients in the ICU have elevated levels of LK-1β, IL-8, IFN-γand TNF-α. This indicates the latent cytokine release syndrome (CRS), analogous to sepsis-associated AKI (SA-AKI), which would result in the uncontrolled systemic inflammatory response and cause kidney injury.

The underlying pathophysiology of kidney impairment in COVID-19 is thought to be multifactorial, for example, with cardiovascular comorbidity and predisposing factors as dominant contributors. As reported, Cardiorenal syndrome shows a strong association with kidney injury. The right ventricular dysfunction secondary to COVID-19 infection may result in kidney congestion and subsequent AKI while low cardiac output, arterial underfilling, and kidney hypoperfusion would be the consequences of the failure of the counterpart-ventricle. Autopsy data demonstrate that the renal endothelium cells are affected, where it is probably accountable for proteinuria and viremia due to the presence of viral particles. Additionally, SARS-CoV-2-related immune response dysregulation (cytokine release syndrome, lymphopenia) as well as other factors including macrophage activation

syndrome, rhabdomyolysis, and the development of microemboli in the context of hypercoagulability and endothelins, may also lead to AKI.

5. Cardiovascular Involvement

Cardiovascular manifestation is very common among patients who are infected with COVID-19. As reported, 86% of respondents experienced cardiovascular symptoms, while the most common reported symptoms were heart palpitations (67.4%), tachycardia (61.4%), pain/burning in the chest(53.1%), and fainting (12.9%). The cardiovascular symptoms are more significant over the first 2 months than in later months, however respondents still suffering from heart palpitation(40.1%), tachycardia(33.7%), and pain/burning in the chest (23.7%) in the seventh month.

One of the most dominant underlying mechanisms is the presence of ACE2 and its distribution. There is a huge amount of ACE2 expression in cardiac tissue, which may potentially facilitate direct myocardial damage induced by viral infection. Studies also reported COVID-19-induced myocarditis expressed in isolated cases, which support the postulation of direct myocardial injury by SARS-CoV-2.In addition, ACE2 catalyzes the conversion of angiotensin II to angiotensin 1–7 in the renin-angiotensin system, which exerts a protective influence on the cardiovascular system. Some agents believe that the binding of SARS-CoV-2 to ACE2 would result in loss of the external ACE2 catalytic effect, as a result, the downregulation of ACE2 and the decrease in angiotensin 1-7 levels would probably impede proper heart function.

The mismatch between myocardial oxygen supply and demand could also contribute to Myocardial injury (type 2 myocardial infarction). SARS-CoV-2 infection along with hypotension, which manifests in sepsis and during the cytokine storm syndrome, may largely influence the supply of myocardial oxygen and causes Severe respiratory complications and associated hypoxia.

6. Cutaneous Manifestations

Whilst the cutaneous manifestations of COVID-19 have been increasingly reported, their exact incidence, as well as the pathophysiological mechanisms, has yet to be estimated. And whether SARS-CoV-2 plays a direct or indirect role in their pathogenesis is still debatable. Additionally, multiple pieces of evidence represent those skin manifestations associated with COVID-19 are extremely polymorphic. One study categorized those COVID-19-associated cutaneous manifestations into the following six main clinical patterns: urticarial rash, confluent erythematous /maculopapular/ morbilliform rash, papulovesicular exanthem, chilblain-like acral pattern, livedo reticularis-like pattern, purpuric”vasculitic” pattern.

7. Post-Acute Sequelae SARS-CoV-2 Infection (PASC)

According to a study, which aimed to establish the long-term effects of COVID-19 following hospitalization and recruited 327 hospitalized patients with SARS-CoV-2 infection and discharged after at least 3 months, the result is followed: 55% of participants reported not feeling fully recovered, 93% reported persistent symptoms, with fatigue the most common (83%), followed by breathlessness (54%). As it shows participants reported significant difficulties which are independent of age and prior comorbidity. The high frequency and severity of long-term symptoms raise the awareness of the importance of long-Covid symptoms and the potential long-term impact on population and wellbeing. All in all, those patients with ongoing symptoms after recovery required instant and comprehensive diagnosis to prescribe treatment and mitigate impairment. The future direction of PASC is clear. First, we need to define the post-viral illness: cardinal features,

duration of disease, inclusion, and exclusion criteria, etc. and record these data, because well-characterized patient registries will be critical for future research. A series of tests need to be done to diagnose the patients and these reports are better to be collaborative on the accessible open database, for the worldwide clinics and hospitals to consult. Fundings and health care resources are needed to be redistributed to those populations with long-term symptoms.

8. Conclusion

In general, the organ-specific manifestations are mainly delineating in 8 organ-related systems. The main contributor is the genetic manipulations of ACE2 expression, which distributes in those body cells and provide a pathway to bind with viral spike protein and ultimately enhancing inflammation. The presence of long-term symptoms and poor long-term outcomes over several months after hospitalization for COVID-19 may have implications for the planning of care and rehabilitation pathway. The government or local community needs to take intensive attention to those patients with persistent symptoms, who need to present to multiple specialties within the health care system unless the community could provide a dedicated long Covid service. Also, the range of syndrome identified highlights a need for long Covid clinics to triage patients for further comprehensive diagnosis and assessing underlying etiology to inform treatment and improve the life quality of un hospitalized patients. There is much previous support for patients with ongoing symptoms, e.g. crowd-sourcing.

Crowd-sourcing, the combination of the words “crowd” and “outsourcing” coined by Howe is defined as an imitated community sharing the solutions for tasks and experiences together. Although the study of crowd-sourcing developed in the information technology field, it has great promise in health, and particularly in global health, given it comprises a rapid, low-cost strategy for reducing uncertainty by openly sharing and analyzing endless amounts of information from an indefinite number of people. This appliance could help patients who lack knowledge and worrying about their well-being to be informed and better treated.

References

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