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REVIEW ARTICLE

THE IDIOSYNCRASY OF SYSTEMS IN COVID-19: REVIEW OF CURRENT KNOWLEDGE.

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Abstract

The COVID-19 requires multidisciplinary approach in diagnosis and treatment as it involves multiple organ systems. This necessitates a need in understanding the involvement of each organ system in disease. This paper aims to capture and provide an overview of the associated symptoms of each system.

Keywords: SARS-CoV2, ACE2, PaO2/FiO2, Immune mediated

Background

The pandemic caused by the novel coronavirus SARS-CoV-2, also known as Coronavirus Disease-2019 (COVID-19), is one to occur in nearly a century since the last pandemic caused by the Spanish flu in 1920. In the hundred years, healthcare has drastically improved and was thought to be prepared to face and control a pandemic. But the corona epidemic which originated in parts of China spread all over the planet in a very short amount of time resulting in a pandemic situation. Many countries follow a different strategy in controlling the spread of the disease and various treatment protocols. But the mode of infection and the pathophysiology of the disease has been identified, the control and treatment of the infection are based on the recent findings on the coronavirus and the knowledge from the Severe Acute Respiratory Syndrome (SARS) virus.

Coronavirus affects the respiratory system through droplets. [1] The infected person spreads the virus by coughing, sneezing, or by leaving traces of viruses on the surface.[1] Pathophysiologically the COVID-19 is manifested as oedema, protein exudates, fibrous tissues, patches of inflammation, and multinucleated giant cells in the tissues and organs of the body. Majority of COVID-19 affected individuals remain asymptomatic or mainly present with respiratory symptoms with fever.[1]

This paper aims to capture and provide an overview of the allied symptoms of each system separately seen in the COVID-19. The articles included in this paper were selected based on the criteria of the recent publication date and system-specific journals. Some articles published in the recent decade on SARS and Middle East Respiratory Syndrome (MERS) were also included as research on the novel coronavirus is limited and is regarded to be very similar to the viruses previously studied.

Structural and functional properties of the virus

The SARS-CoV-2 virus responsible for the COVID-19 pandemic is a single-stranded RNA virus of family Coronaviridae which affects humans, birds, and other animals. Only alpha-coronavirus and beta-coronavirus are known to infect humans and other mammals. The well-known epidemics of recent times, namely, the MERS and the SARS, were caused by beta-coronaviruses. The coronavirus that caused the COVID-19 pandemic is believed to be a mutated virus from bats that had developed mutations in the receptor-binding function, along with a protease cleavage area. [2]

Two subunits of the structural S gene of the coronavirus is responsible for the receptor binding. [2,3] The subunit S1 is responsible for binding with the target cells, while the subunit S2 is responsible for the fusion to the target cells. Interestingly, the subunit S1 contains two domains namely, N- and C-terminals. The terminals are responsible for the binding of the virus to various receptors containing carbohydrate or protein domains. [3] The infection of coronavirus is associated with Angiotensin Converting Enzyme-2 (ACE2), which plays a significant role from the point of infection to the progression of the disease.

Respiratory system

The COVID-19 manifests mainly in the respiratory system by reducing the respiratory functions, resulting in dyspnoea and hyperpnoea with a rate of more than 30/minute. The blood oxygen saturation (SpO2), which should ideally be around 99%, falls less than 93% in severe cases. [4] Also, the P aO2/FiO2 ratio falls below 300. It is noted that about 15% of individuals affected by COVID-19 develop pneumonia with lung infiltrates of more than 50% within 48 hours. [4] Among COVID-19 diagnosed individuals, 5% develop severe respiratory symptoms and ultimately result in respiratory failure and in some

cases with septic shock leading to multi-organ failure. [4]

It is believed that alveolar epithelial type-2 cells express a high level of ACE2 and could potentially act as a reservoir for the coronavirus. This cell is also thought to aid in viral replication and disease progression.[5] Pneumonia-induced hypoxia increases the viscosity of the blood by hypoxia-induced transcription factor-dependent pathway, which promotes thrombolytic activity, which later acts as a factor in the severity of the disease.[6]

Nervous system

In the brain, the nuclei present in the subfornical organ, nucleus tractus solitaries, rostral ventrolateral medulla and paraventricular nucleus regulate the cardiovascular functions are affected. [7] Headache is inversely related to age and women are the most affected in the disease.[7] A history of migraine was associated with the headache caused by COVID-19.[7] The character of headache varied from mild to severe headache similar to tension headache or migraine headache. The headache and anosmia seen among the cases are due to the direct involvement of afferent branches of olfactory and trigeminal nerves. [7] Some patients suffering from COVID-19 also reported encephalopathy, encephalitis and Guillain-Barre syndrome, of varying severity.[8]

Endocrine system

Many endocrine organs express ACE2, and the coronavirus affects the associated endocrine organ. COVID-19 through ACE2 receptors cause a clinical picture of hyperglycaemia by the effect on pancreatic beta cells. Acute onset diabetes was noted among the infected who were healthy before and led to the development of ketoacidosis and changes in blood osmolarity.[9] The hyperglycaemia and other elevated pancreatic enzymes seen among COVID-19 cases could be due to stress related as some studies done on SARS suggest.[10] On the contrary, a hypothesis suggests that SARS express Adrenocorticotropin Hormone (ACTH) mimicking sequence of amino acids, thus leading to a reduction of stress-induced cortisol by the destruction of circulating ACTH, ultimately reducing the cortisol stress response of the body.[5] The BMI of the individual could also potentially pave the way for the severity of the infection as the adipose tissue is known to express ACE2, thus suggesting that obesity increases morbidity and mortality due to COVID-19. [10,11]

The positive pressure ventilation (PPV) maintained among the COVID-19 cases during the in-patient care leads to the syndrome of inappropriate antidiuretic hormone (SIADH) and low blood sodium. [12] The effective blood volume reduces in PPV, thus the pulmonary vessels receive less blood. The reduced blood supply through baroreceptors of the pulmonary veins stimulates Antidiuretic Hormone (ADH) secretion. The ADH secretion is believed to be non-osmotic in nature. [12]

Immune system

The systemic inflammation seen in the coronavirus infection is due to IL-1, IL-6, Monocyte chemoattractant protein-1 (MCP1), and other immune mediators which promotes inflammation of multiple organ tissues. [13] The systemic inflammation is less in the early stages of the disease and is progressive when the treatment is not initiated early for high-risk populations. Some cases reported secondary cytokine storm syndrome which is characterised by fever and hyper-inflammation.[13] In severe cases, the disease progresses to multiple organ failures and ultimately, loss of lives. The multiple organ damage and failure can be attributed to the cytokine storm seen in macrophage activation syndrome, an immune response to fight against the infection.[13] One interesting hypothesis suggests that inhibition of Interferon type-1 (IFN-1) rapid expression leads to loss of initial defence of the coronavirus infection, thus leading to the severe progression of the disease. [8] Similarly, SARS is known to hinder IFN-1 through interfering with STAT-1 phosphorylation signalling pathway to delay IFN-1 response. [14]

Cardiovascular system

Though COVID-19 infection mainly manifests in the respiratory system, co-morbidities associated with the cardiovascular system significantly increases the mortality. [2] It is believed that the cardiomyocytes are affected by the coronavirus after proteolytic cleavage of the S protein of the virus, which then enters the cell by binding to the ACE2 resulting in damage of myocardium.[2] ACE2 has been identified to promote the viral invasion into the cells. Hypertension was not found to be a predisposing factor in acquiring the disease and is considered merely an association as the risk group for the coronavirus infection is old age and the older population tends to have hypertension. [2] A study found that patients with heart failure expressed more ACE2 receptors due to up-regulation of it.[15] This up-regulation of ACE2 receptors may explain the severe course of the infection among patients with heart associated comorbidity. [15] The virus after spreading from the lung parenchyma is also found in plasma, suggesting a haematogenic way of spreading to other organs.[15]

Renal system

Patients affected with COVID-19 are known to suffer from acute kidney injury manifested by proteinuria, haematuria, and creatinine presence in urine.[16] The exact mechanism behind the progress of the disease is still under investigation, but ACE2 is still considered the path through with COVID-19 affects the kidneys. In kidneys, the ACE2 receptors are found in proximal tubules, glomerular podocytes and capillary endothelial cells. [17] Meanwhile, severe cases of COVID-19 were found to be in a hypercoagulable state, thus resulting in increased usage of coagulation factors, where a clinical picture of disseminated microvascular thrombosis is frequently met.[16] The management of patients undergoing haemodialysis differ from the non-haemodialysis patients in COVID-19 treatment, as the former are susceptible to severe infection.[18]

Gastrointestinal system

Non-specific intestinal symptoms such as abdominal pain, vomiting, and diarrhoea were noted among the cases. The gastrointestinal epithelial cells express ACE2 receptors and suggest the connection in the viral replication. Like the SARS virus, SARS-CoV-2 was also found in stool examination and in biopsy. [19] A positive stool examination was seen in patients even when the nasal swab test for COVID-19 was negative. Some cases also had abnormal liver function test in aspartate aminotransferase, alanine aminotransferase and G-glutamyl transferase levels suggesting liver damage. [19] The liver is thought to be affected due to a combination of direct affection by the virus, the immune response mediated injury of the hepatocytes and due to medications. [19]

Reproductive system

Among males, ACE2 receptors are associated with spermatogenesis and steroidogenesis; and are known to be present in human testes and epididymis, mainly on the Leydig and Sertoli cells. [10] It was also found that the expression of ACE2 is highest in the testes10. Any involvement of the hypothalamic-pituitary-adrenal axis could suppress luteinizing hormone (LH) and follicle-stimulating hormone (FSH). A study among COVID-19 patients found to have normal testosterone but increased LH. [20]

A study conducted among pregnant women in their third trimester found no evidence of COVID-19 being vertically transmitted to the foetus and in most cases, the baby was born rather normal with normal vital signs.[20] The data on COVID-19 infection and early pregnancy is not conclusive in illustrating the effect of vertical transmission. But the possibility of miscarriages and preterm delivery are not ignored as SARS infection documented the said complications among pregnant women during early pregnancy. [21]

Integumentary system

Though understudied, skin manifestations in COVID-19 are vital in understanding the clinical picture, perhaps for early diagnosis. A study conducted in Spain, one of the worst-hit nations during the initial period of the pandemic, found around one-fifth of the patients showed skin manifestations during the course of the disease or even before being symptomatic. [22] Some of the skin manifestations among COVID-19 positive patients include skin rashes of maculopapular or vesicular in nature, urticarial lesions, pityriasis, livedo reticularis and vesicular chilblain lesions. [22] Most of the skin rashes resembled infection from a virus that has clinical manifestation on the skin and was localized mostly on hands and feet. [23]

Along with the skin manifestation of the coronavirus infection, increased use of alcohol-based sanitizers, excessive and unnecessary cleaning of hands and other exposed part of the body, and use of personal protective equipment including latex gloves and face masks results in non-COVID dermatitis, pruritis and folliculitis. [23,24]

Conclusion

At the time of this article being written, no vaccine has been proved to be clinically effective for use against the virus. Countries follow their own treatment strategies but mostly include antiviral, antibiotic, and steroid therapy. Most countries have mandated strict hygiene rules and frequent disinfection of public places and plan to continue till an effective preventive measure is available. With a new vaccine, comes new speculation surrounding its effectiveness and efficacy in preventing the infection, which prompts better public education of the disease. Meanwhile, more research into the clinical features of the disease for early diagnosis, prevention of new cases and reinfection is being carried out every day to equip the medical services to face the current pandemic situation and prevent one in the future.

Author Contributions

R-SS and K-S contributed for the collection of related articles, conceptualization and draft preparation. P-KM contributed for conceptualization, decision of topic, and critically reviewed the manuscript.

Conflict of Interest

The authors declare no conflicts of interest in the publication of this article.

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