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REVIEW ARTICLE

Non-Respiratory Manifestations of COVID-19 and Pathophysiological Evidences

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Abstract:

Globally, COVID-19 is a viral disease that has become a public health challenge in 2020. COVID-19 is caused by a novel coronavirus, SARS-CoV 2, that was first discovered in the Hubei province of China and it commonly manifests as a respiratory illness but also with symptoms ranging from mild myalgia to severe pneumonia. As our primitive understanding of this novel virus has evolved, COVID-19 has been shown to present in atypical non-pulmonary clinical manifestations, such as diarrhea, acute kidney injury, hepatic and cardiovascular abnormalities, blood coagulation and stroke along with loss of some special senses. We consolidated the publicly available information to precisely summarize the knowledge about the significant non-respiratory clinical manifestations of COVID-19.

Keywords: COVID-19, Non-respiratory, Atypical symptoms, Viral disease, Novel virus, Pathophysiology.

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1. INTRODUCTION

The World Health Organization (WHO) has announced in 2019, that the corona virus disease (COVID-19) is a pandemic disease that has aroused international attention and public health emergencies [1].The novel corona virus SARS-CoV-2 causes COVID- 19 which is predominantly respiratory tract infections. More than 4 million cases of COVID-19 have been confirmed worldwide and although most of the people are present with cough, fever, and difficulty in breathing but some people are experiencing new clinical symptoms. Non-respiratory symptoms include diarrhea, abnormal renal function, and potentially life-threatening thrombus. It is uncommon for respiratory viruses to have such widespread influences in the body.

An earlier research study has revealed that non-pulmonary symptoms may also be good indicators of SARS-CoV-2. Once the corona virus enters into the human body, it will attach to a protein called angiotensin-converting enzyme 2 (ACE2) on human cells. This enzyme is usually involved in blood pressure regulation and is located on the surface of different types of cells, including brain cells, blood vessels, heart, intestines, and kidneys [2].

In this review, we briefly discussed the basic pathophysiological knowledge of corona virus in other systems of human body and its non-respiratory clinical manifestations and possible risk factors. Our understanding regarding COVID-19 is still growing rapidly, and the further review will explore the uncommon clinical features of corona virus in other major body systems, along with its association with hypercoagulability, stroke, and special senses. Understanding the various symptoms of COVID-19 on the non-respiratory system is essential to provide comprehensive medical services to infected patients.

2. GASTROINTESTINAL SYSTEM

Recently, SARS-CoV-2 RNA was detected in a stool specimen which led to a suspicion of viral gastrointestinal infection and a fecal-oral transmission route [3]. SARS-CoV-2 uses an angiotensin-converting enzyme 2 (ACE 2) as a viral receptor for its entry process in the body which is abundantly expressed in intestinal cells [4]. The sodium-dependent neutral amino acid transporter OAT1 in the gastrointestinal tract stabilizes the over-expressed ACE 2 messenger RNA that facilitates SARS-CoV-2 infection [5, 6].Because ACE2 expression is found in both the upper and lower gastrointestinal tract, so its expression level is nearly 100 times higher in GI than that of respiratory organs. Besides this, over half of the patients who are infected with COVID-19, have the viral nucleic acid detected in feces [7], and nearly 25% of the stool samples showed test positive when respiratory samples were negative [8, 9].

The potential risk factors for developing GI infection of

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COVID-19 are chronic diseases like inflammatory bowel disease. In 29 studies (6064 cases) reporting gastrointestinal symptoms in patients with COVID-19, the prevalence of digestive symptoms was 15% and the most common were nausea or vomiting, diarrhea, and anorexia. The authors also reported that around 10% of patients presented with gastrointestinal features without respiratory symptoms [10]. Another study involving 204 COVID-19 positive patients showed that 103 patients (50%) presented with digestive symptoms, such as lack of appetite (79%), diarrhea (34%), vomiting (4%), and abdominal pain (2%) [11]. These reports imply that in some patients, although SARS-CoV-2 gets cleared in the respiratory tract, the virus continues to replicate in the gastrointestinal tract and could continue to be shed in feces leading to potential problems for themselves and individuals with whom they came into contact [10].

The impact of COVID-19 on the GI system may have a particularly distressing effect on patients as they are inclined to suffer longer and infections are detected later. Diarrhea lasts from 1 to 14 days, with an average of 5 days [9]. When a patient is infected, it takes an extended time to clear the virus. A study in China showed that 41 (55%) of 74 patients had SARS-CoV-2 RNA-positive fecal samples and while the respiratory samples of these patients remained positive for a mean of 16·7 days, their fecal samples remained positive for a mean of 27·9 days. One patient had RNA-positive fecal samples for 33 days after their respiratory samples became negative [12].

3. RENAL SYSTEM

Kidney cells also carry the ACE2 receptors. A review of electronic health data of more than 5,000 COVID-19 hospitalized patients showed that 36.6% of known COVID-19 patients have acute kidney injury, and 14% of 1,830 patients require dialysis support for sustaining kidney function. The SARS-CoV-2 virus may also affect the kidney in one or two ways via the ACE2 receptor as it could directly infect kidney cells or trigger an aggressive systemic inflammatory response in the body. Kidney damage is directly related to the worsening of respiratory symptoms; almost 90% of people who require mechanical ventilation and only 22% of people who do not, develop acute kidney injury [13].

These numbers are far higher than the incidence in regular hospitalized patients as shown in a study with 19,249 patients in whom an AKI incidence of 21% was observed, out of which almost 60% of AKI occurred in patients who never received care in an intensive care setting. [14] Patients with kidney disease have a significantly higher risk of in-hospital mortality, and the risk varied significantly due to independent risk factors [15].

4. HEPATIC SYSTEM

The liver also contains ACE2 receptors. Laboratory studies using cells in Petri dishes have shown that SARS-CoV-2 can enter and infect liver cells through these receptors. A previous study including 99 SARS-CoV-2 infected patients revealed that 43 out of them, had elevated levels of the liver enzymes - alanine aminotransferase, aspartate aminotransferase, and lactic dehydrogenase, which are the signs of liver damage [16]. A study of 417 covid-19 patients with at least one abnormal liver function test was conducted, of which more than 90% of patients had mild to moderate symptoms at the time of admission, and about 24% of them developed increased ALT and GGT levels to substantially more than 3 times the Upper limit of normal during hospitalization. It was discovered that after admission, the use of drugs, especially lopinavir and ritonavir, was the most important risk factor for liver damage. The use of lopinavir/ritonavir increased the odds of liver injury by 4-fold [17].

The most common presentation is acute hepatitis. Predisposing risk factors are chronic illnesses like liver cirrhosis, chronic cholestatic liver disease, and liver transplantation recipients. The more severe the condition, the greater the likelihood of them developing coagulopathy and fulminant hepatitis [18].

However, only a few cells express ACE2 in the liver, so it is unclear whether the virus causes the damage directly or via a cytokine storm that may affect the liver [19].

5. CARDIOVASCULAR SYSTEM

American College of Cardiology issued a clinical bulletin which revealed that the COVID-19 mortality rate of patients with cardiovascular disease was found to be 10.5%. The data also indicates that people over 65 years of age who are more likely to have underlying coronary artery disease or high blood pressure are highly susceptible to be infected with the virus [20]. Heart muscle cells express numerous ACE2 receptors. The severity of heart muscle involvement, in most cases, is directly related to the severity of lung involvement. The presence of any co-morbidity will multiply the risk of death by 12 times [21, 22].

A recent study which included 191 patients from Wuhan, China, confirmed that 48% of patients had any co-morbidity, like hypertension was found in 30%, DM accounted for 19%, and cardiovascular disease was present in 8% [23]. The vulnerable groups are those with pre-existing established cardiovascular diseases. In COVID-19 patients, cardiovascular complications are common, and are associated with higher risk of morbidity and mortality.

Common cardiac complications are hypotension, myocarditis, arrhythmias and sudden cardiac death. Post-mortem autopsy reports of some patients illustrated myocardial infiltration by interstitial mononuclear inflammatory cells [24]. COVID-19 patients with cardiac involvement have elevated cardiac biomarkers secondary to infection-induced myocarditis and ischemia [25]. It has also been linked with long term implications due to systemic inflammatory activity.

Cardiovascular diseases can also be secondary to acute lung injury which in-turn cause increased cardiac workload, which can be deleterious in patients with pre-existing heart failure. Immune system activation results in plaque instability, contributing to acute coronary events.

Acute myopericarditis in COVID-19 was reported few days after symptoms of fever, fatigue and dry cough emerged with ECG showing diffuse ST elevation. Arrhythmias in

COVID-19 are rare occurrences and mostly associated with myocardial infarction, electrolyte imbalances and drugs causing QT prolongation including hydroxychloroquine used in COVID prophylaxis [26].

6. HYPERCOAGULABILITY AND STROKE

One of the emergent risk factors during this pandemic is related to blood clots, including those that may cause a stroke. Similar to lungs, kidneys, liver, and intestinal cells, vascular cells are also expressed with ACE2 receptors, which means that the virus may directly infect blood vessels which leads to blood coagulation.

The largest and most comprehensive analysis of COVID-19 patient's autopsies revealed that the brain showed surprisingly sparse inflammation, and only a few cases showed small focal areas of chronic inflammation. However, it is surprising that many cases showed micro thrombosis. These small infarctions may provide an explanation for the psychological changes in some of the positive patients [27].

Two studies detailing the incidence of thromboembolic complications in SARS-CoV-2 patients have shown that the incidence of ischemic stroke is between 1.6% [28] and 2.5% [29]. Other risk factors make SARS-CoV-2 patients prone to thromboembolic stroke, the incidence of which exceeds traditional cardiovascular and metabolic comorbidities, and complications associated with long-term hospitalization in the intensive care unit.

Also, history noted that large vessel strokes were related to the SARS-CoV-1 epidemic in 2004 [30]. It has also been suggested that coagulopathy and vascular endothelial dysfunction are a complication of COVID-19 [31].

Studies have shown that COVID-19 patients have abnormal blood coagulation pathways, including elevated D-dimer [32 - 35]. The study of 25 patients with COVID-19 pneumonia found that all patients had elevated D-dimer, with a median of 6.06 micrograms/ml, of which 10 cases were diagnosed as pulmonary embolism (PE) by computed tomography pulmonary angiography (CTPA) [34]. The median D-dimer level of patients confirmed by CTPA as PE was 11.07 μg/ml [34]. Patients with D-dimer levels greater than 1 μg/mL and COVID-19 increased the risk of death during hospitalization. A study showed that anticoagulation therapy, mainly the low molecular weight heparin, may contribute to a six-fold reduction in mortality from D-dimers greater than the upper limit of normal [36].

7. NERVOUS SYSTEM

Among 31 neurological studies on COVID-19 patients, 7 reported on Guillain-Barre syndrome, 11 reported on headache, 5 reported on olfactory dysfunction, and 5 reported on acute cerebrovascular accidents.

It has been proposed that SARS-CoV-2 gains entry to the CNS by one of two ways: firstly, by systemic vascular dissemination and, secondly, more locally across the cribriform plate of the ethmoid bone. Once entered in the systemic circulation, the virus invades neural tissue due to its properties of neurotropism. Here, it binds to and interacts with angiotensin-converting enzyme 2 (ACE2) receptors in the capillary endothelium [37].

The long-stay admissions in the hospital that patients with severe COVID-19 are currently experiencing may also pose another issue, that is post-intensive care syndrome (PICS), and in particular critical illness polyneuropathy and myopathy (CIPNM).

However currently, no direct cause and effect has been attributed to neurological deterioration in patients with SARS-CoV-2 and this relationship could just as plausibly be explained by association with other multi-organ system failures. The direct effect on mortality and morbidity in such “neurological involving” patients is yet to be elucidated [37].

Children have been seen to be less likely to become severely ill, but SARS-CoV2 should be considered in patients of the young age group presenting primarily with neurological symptoms without any obvious systemic involvement. There are multiple reports of children presenting with systemic inflammatory response requiring intensive care in contrast to many who presented with a less severe Kawasaki-like illness [38]. In UK, a cohort study of 58 children who presented with inflammatory multisystem syndrome showed that 4 children were confirmed with COVID-19 who had distinct neurological presentations with lesions of splenium of corpus collosum (SCC) [39]. Previous studies showed that reversible lesions of the SCC suggest an underlying intramyelin edema secondary to inflammatory response. Such a typical, transient lesion is also seen in pediatric population with Kawasaki disease [40]. The response to immunosuppressant in these children along with the clinical overlap with hemophagocytic lymphohistiocytosis impresses upon us to conclude that the neurological symptoms of SARS-CoV2 have not demonstrated neurotropism and that the underlying mechanism can be attributed to an immune-mediated response [39]. Very meticulous neurodevelopment surveillance is mandated for these children

8. SPECIAL SENSES

Another group of intriguing reports from people affected by COVID-19 has to do with an increasing body of significant anecdotal evidence suggesting anosmia as being a symptom of SARS-CoV-2. Olfactory disturbances may lead to changes in taste. A recent study indicates that before COVID-19 diagnosis, 73% of the subjects noticed insomnia, and in 26.6% of the subjects, it was the initial symptom [41].

In Korea, a survey found that 15.3% of the 3191 confirmed SARS-CoV-2 cases had lost sense of smell or taste [42]. German virologist, Hendrick Streeck reported that more than two-thirds of the patients with mild symptoms of COVID-19 revealed that they had lost their sense of smell and taste [43].

There are some other cases reported that conjunctivitis is also related to COVID-19, but these symptoms are rare. Nevertheless, some researchers still want to know whether the virus can enter the body through the eyes. In a small study in China, researchers have discovered viral RNA in people’s tears. Another study in China which was conducted on 38 COVID-19 positive patients, revealed the presence of SARS-CoV-2 virus in conjunctival specimen of 5.2% patients [44].

Eye cells do express the ACE2 receptor, but researchers still believe that eye-related infections or tear-associated virus transmission can occur and are very rare.

CONCLUSION

Patients with COVID-19 are typically present with cough, fever and other respiratory symptoms. But, in recent weeks, the extensive research on COVID positive patients has revealed an unexpected array of symptoms manifesting as other systemic illnesses. In the absence of vaccines or curative medical treatment, COVID-19 exerts an unprecedented global impact on public health and health care delivery. This review provides an insight into the current COVID-19 state of the art in terms of various non-respiratory clinical manifestations including gastrointestinal, renal, hepatic, cardiovascular, hyper-coagulability, nervous and special senses involvement. Physicians must follow up the patients and look for early signs of complications or delayed recovery of the affected organs to normal so that a prompt intervention can be initiated. Physicians must also be aware of the uncommon modes of transmission in order to reduce community spread and also provide awareness. There is a rapidly growing body of literature and ongoing research in this field which hopefully will help in elucidating an effective best protocol for the management and treatment of atypically symptomatic patients.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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