REVIEW

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COVID-19 – multisystem disease

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), caused a global public health crisis, with a significant impact on multiple body systems. This virus, a member of the *Coronaviridae* family, shows ~80% genomic similarity to SARS-CoV and ~50% genomic similarity to Middle East respiratory syndrome coronavirus (MERS-CoV). The spike (S) protein plays an essential role in the pathogenesis of the virus, as it facilitates its entry into host cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. In addition to the respiratory system damage, SARS-CoV-2 infection causes a variety of gastrointestinal (GI), neurological, cardiovascular (CV), ocular, renal, etc. clinical manifestations. Neurological complications, such as anosmia, ague, headache, encephalitis and cerebrovascular events, were frequently observed, being attributed to both direct viral invasion and a very strong systemic inflammatory response. GI symptoms such as diarrhea, nausea and vomiting are common and may occur independently of respiratory symptoms, and the presence of viral ribonucleic acid (RNA) detected in fecal samples suggests possible fecal-oral transmission. The CV system is affected by myocardial damage, inflammation and coagulation disorders, with an increased risk of thromboembolic events. At the ocular level, the virus was identified in ocular secretions, and conjunctivitis, uveitis and episcleritis were observed in about 11% of patients. Renal involvement, manifested by acute kidney injury, was detected in 0.5–7% of cases. In conclusion, SARS-CoV-2 infection is not limited to respiratory tract involvement but also has significant systemic implications.

Keywords: COVID-19, SARS-CoV-2, virus, digestive system, neurological complications, spike proteins.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19) disease, is one of the most significant global public health challenges [1]. SARS-CoV-2 first occurred in Wuhan, China, in late 2019, from where it rapidly spread worldwide [2]. Coronaviruses belong to the *Coronaviridae* subfamily and based on genotypic and serological properties they are classified into four genera: alphacoronaviruses, betacoronaviruses, deltacoronaviruses and gammacoronaviruses [3].

The SARS-CoV-2 genome sequence shows ~80% similarity to SARS-CoV and ~50% similarity to Middle East respiratory syndrome coronavirus (MERS-CoV) [4, 5]. SARS-CoV-2 is a positive-sense single-stranded ribonucleic acid (RNA) virus with a genome length of less than 30 kb [6]. Four major structural proteins are encoded in the SARS-CoV-2 genome: membrane (M) proteins, envelope (E) proteins, nucleocapsid (N) proteins and spike (S) proteins, which are different from those found in the SARS-CoV genome [7, 8].

In the pathogenesis of the virus, the most important are the S proteins that are located on the outer surface of the virus and play a crucial role in infection, as they mediate virus entry into host cells by binding the virus particle to a receptor for angiotensin-converting enzyme 2 (ACE2) on the cell surface and then cause virus entry into the cell [9].

Multiple studies showed that the C-terminal domain of the S protein exhibits a higher binding affinity for the ACE2 receptor [10].

The crown-like aspect of the virus is given by the S protein, which is assembled as a homotrimer and imprints multiple copies into the virion membrane. At virion maturity, the S protein displays two subunits that are non-covalently associated, namely the S1 subunit that binds to ACE2, and the S2 subunit that is responsible for the attachment of the S protein to the membrane [11].

The activation of the viral S protein, which allows fusion with the host cell membrane, is thought to be crucial for entry

into the host cell. Through the enzymes, transmembrane serine protease 2 (TMPRSS2), cathepsin B or L (CTSB or CTSL), and furin, which are found on the host cell membrane, cleavage of the SARS-CoV-2-specific S protein is achieved [12].

Respiratory system involvement

Although COVID-19 causes multiorgan damage, the main clinical manifestations are in the lung, ranging from lung failure, pulmonary embolism and secondary bacterial pneumonia to pulmonary fibrosis [13].

SARS-CoV-2 infection is primarily a lung disease, which can manifest as symptoms of both acute upper and lower respiratory tract syndrome, with varying degrees of severity. Unlike influenza, which tends to start suddenly, the symptoms of SARS-CoV-2 infection may present a more gradual onset. Patients may be asymptomatic in the initial stage of infection, or they may present with a self-limited syndrome that is characterized by fever, fatigue, muscle aches, joint pain, rhinorrhea, sore throat and/or conjunctivitis [14]. However, in severe infections, SARS-CoV-2 can trigger an excessive inflammatory response, known as a 'cytokine storm', which exacerbates tissue damage thereby inducing acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure [15, 16].

Bilateral pneumonitis is present in the majority of patients with COVID-19, and unilateral pneumonitis is present in a small number of patients. The most common findings on computed tomography (CT) examinations are irregular bilateral opacities with a "frosted glass" aspect. Multiple lobar involvement and the presence of focal lesions such as spots, streaks or nodules are also common [17].

Neurological manifestations

In patients infected with SARS-CoV-2, neurological dysfunctions were detected, thus suggesting that the virus affects not only the encephalon but also the peripheral nervous system, through the presence of the ACE2 enzyme in both the encephalon and the peripheral nervous system [18].

Neurological manifestations present in SARS-CoV-2 patients include olfactory and gustatory dysfunction, anosmia, ageusia, acute headache, seizures, encephalitis, and muscle rigidity [19].

Headache is one of the most common neurological manifestations in patients with COVID-19, present in both mild and severe forms of the disease [20].

The loss or decrease in the olfactory (sense of smell) and gustatory senses in patients with COVID-19 is probably caused by SARS-CoV-2 infection of cells in the nasal and buccal mucosa [21, 22]. Studies show that high concentrations of the ACE2 receptor are found in epithelial cells in the olfactory, nasopharyngeal and buccal mucosa [23, 24]. By binding to this receptor in the nasal and oral mucosa, SARS-CoV-2 could disrupt the function of sensory cells responsible for detecting odors and tastes, leading to disturbances in these senses [19].

SARS-CoV-2 infection involves an increase in inflammatory cytokines that favor thrombus formation, while the penetration of inflammatory cells into the vascular endothelium produces both endothelial and platelet activation which increases the risk of thromboembolic events [25].

A case study reported the presence of *status epilepticus* in COVID-19 positive confirmed patients, even in the absence of severe respiratory symptoms. This suggests a possible direct involvement of the virus on the nervous system [26].

Encephalitis is an inflammation of the brain parenchyma, manifested by confusion, fever, headache, seizures [27].

Gastrointestinal lesions

In addition to the respiratory tract, SARS-CoV-2 infection also affects the digestive tract, so patients with COVID-19 have gastrointestinal (GI) symptoms that may occur before or after respiratory symptoms. Commonly reported digestive symptoms may include anorexia, nausea, vomiting, and diarrhea, the latter of which is, in some cases, the first symptom of patients with COVID-19.

GI imaging tests reported changes such as thickening of the intestinal wall, sometimes with hyperemia, fluid-filled large bowel and sometimes pneumatosis and ischemia [28].

An analysis that combined the results of 60 studies of a total of 4243 patients showed that, on average, 17.6% of patients experienced GI symptoms. The most common symptom was anorexia, reported in 26.8% of patients, followed by diarrhea (2.5%), nausea and vomiting (10.2%) and abdominal discomfort (9.2%) [29].

Adequate nutrition plays an essential role in the recovery process of patients. A dysfunction of intestinal digestion and absorption processes, predominantly manifested by intolerance to enteral nutrition and exacerbation of diarrhea, leads to nutritional deficiency and malnutrition, resulting in a deterioration of the general health [30].

Typically, GI clinical symptoms and signs are present in patients with concurrent respiratory symptoms. According to one study, GI symptoms preceded respiratory symptoms in 13% of cases, had a synchronous onset in 44% of cases, and followed other COVID-19 associated symptoms in 42% of cases [31]. In various studies, 4–20% of patients presented with GI symptoms exclusively [32]. Patients with GI symptoms alone may have a longer time interval between symptom onset and admission to the medical facility [33].

Although the main route of transmission of SARS-CoV-2 is through respiratory droplets, SARS-CoV-2 RNA was also identified in feces [34]. Clear evidence to support fecal-oral transmission is still lacking but data that are in the process of consolidation support this hypothesis. SARS-CoV-2 RNA was identified in anal swabs and fecal samples in more than 50% of patients with confirmed infection [35]. It is also noteworthy that the presence of digestive symptoms, especially diarrhea, is correlated with an increased prevalence of viral RNA detection in fecal samples, as well as a significantly higher viral load of SARS-CoV-2 RNA [36].

The GI system is affected by SARS-CoV-2 by infiltrating host cells *via* ACE2 receptors, a process that has an increased efficacy, accomplished in three ways: the S protein exhibits a high binding affinity to the receptor, evasion of the immune system by limiting receptor-binding domain (RBD) exposure to the extracellular environment, and early activation of the furin protease before reaching the host cells [37].

The ACE2 receptor is well defined at the GI level, being stabilized by the neutral amino acid transporter B0AT1, which is found in the intestinal epithelium; at this level, in intestinal epithelial cells, ACE2 is essential for maintaining amino acid homeostasis, regulating the expression of antimicrobial peptides and maintaining the balance of the ecology of the gut microbiome. Thus, dysfunction of ACE2 may cause disruption of these processes as well as an increased risk of inflammation [38].

The impact of ACE2 receptors along the GI tract results in symptoms associated with diarrhea and intestinal inflammation [39].

Also, several studies showed that a higher incidence of liver injury is also present in patients with COVID-19, ranging from 2% to 11% [40]. Liver injury observed in COVID-19 patients may be secondary to direct viral infection of hepatocytes or may be caused by other pathogenetic mechanisms, such as pharmacologically induced hepatotoxicity or pneumonia-associated hypoxia [41].

Cardiovascular injury

Cardiovascular (CV) complications associated with influenza virus infection, including myocarditis, acute myocardial infarction, and exacerbation of heart failure, are recognized as contributing factors to mortality during SARS-CoV-2 infection [42].

The presence of viral infections in the body may lead to adverse CV manifestations by supplementing metabolic demand in fixing the limited cardiac reserve or by accelerating plaque rupture in the presence of a prothrombic state and inflammation [43]. In acute myocardial infarction, severe respiratory infection was identified as a risk factor, both in influenza and non-influenza virus infections [44].

In patients with COVID-19, prothrombin levels increase as the disease progresses [45], in some situations exceeding the usual values seen in type II myocardial infarction [46]. These patients show elevated levels of C-reactive protein, which tends to increase simultaneously with troponin, leading to the conclusion that a hyperinflammatory state is involved in the development of non-ischemic myocardial injury [47].

Myocardial injury may occur in the context of exposure to acute stressors such as infection, hypoxemia, anemia, hypotension or shock, acute renal failure and congestive heart failure. Therefore, the development of myocardial injury is frequently observed among patients hospitalized with COVID-19 [48].

In a study looking at myocardial injury associated with COVID-19, 23% of hospitalized patients were found to have heart failure. This was observed in 52% of patients who died and 12% of those who recovered and were discharged. Heart failure was significantly more common in patients who did not survive (52%) compared to those who survived (12%) [49].

One way in which SARS-CoV-2 directly affects the heart and the vascular system is by directly infecting myocardial or other cells of the heart, thereby causing cytopathic effects as well as tissue destruction [49]. 48% of patients who underwent autopsy revealed thrombus or inflammation in the heart vessels, showing that cytopathic effects on cardiac vessels create a predominant mechanism [50].

Another method of cell infiltration is realized by using the membrane surface enzyme ACE2 as a receptor. This enzyme is present throughout the CV system including the heart, endothelial cells, macrophages, fibroblasts, smooth muscle cells [51]. In patients suffering from hypertension and diabetes mellitus, serum ACE2 levels were positively associated with systolic blood pressure values [52].

COVID-19 was repeatedly associated with the presence of inflammation in the CV system, microvascular dysfunction and ischemia, as well as myocardial injury, known to cause cardiac arrhythmias [53]. Atrial fibrillation, tachycardia or ventricular fibrillation are the most important of these arrhythmias.

A major characteristic and significant factor of morbidity in hospitalized patients was the presence of a hypercoagulable state and subsequent pathologies associated with the coagulation process [54]. This condition coexisting with a severe disease caused by COVID-19 infection was accompanied by a proinflammatory state, which affected endothelial cells, leading to disruption of hemostasis. This process triggers an increase in both arterial and venous thrombogenicity [55].

Acute viral infections, such as those caused by SARS-CoV-2, are correlated with the triggering of inflammatory, prothrombotic and procoagulant reactions, which contribute significantly to the increased risk of acute coronary syndrome through coronary plaque instability and thrombus formation [56].

An increased number of CV complications was observed not only in cases where patients had a history of CV disease or hospitalization was required during active infection, but also in patients without comorbidities. However, the severity of SARS-CoV-2 infection is associated with possible postinfection CV complications [57]. Sometimes, CV manifestations in COVID-19 mimic other ischemic, inflammatory, or tumor-related cardiac diseases [58, 59].

Ocular lesions

The prevalence of ocular manifestations is estimated to be approximately 11%, and the most common symptoms include dry eye or foreign body sensation, redness, tearing, eye pain and discharge [60]. In general, damage to the external eye is more common and presents in forms such as follicular or pseudomembranous conjunctivitis, keratoconjunctivitis and episcleritis [61].

Conjunctivitis is the most common ophthalmological lesion associated with SARS-CoV-2 infection [62]. A study published in *JAMA Ophthalmology* [63] reported that approximately one-third of patients infected with SARS-CoV-2 had symptoms of conjunctivitis, including conjunctival hyperemia, chemosis, epiphora, and increased secretions [63]. The virus was detected in ocular secretions, suggesting that the eye may be a pathway for the infection to enter the body [64].

A study conducted in Iran on 142 patients with COVID-19 showed that the most common ocular finding was conjunctival hyperemia (44 patients; 31%). However, in patients hospitalized in intensive care units (ICUs), the predominant ocular manifestation was chemosis (17 out of 28 ICU patients; 60.7%), and 50% of these patients (14 out of 28) had conjunctival hyperemia [65].

Uveitis, representing an inflammation of the vascular layer of the eye, was reported in patients with COVID-19 [66]. Mazzotta & Giancipoli [67] reported a case of anterior uveitis and bilateral conjunctivitis in a 30-year-old female patient, who at the time of presentation had bilateral ocular redness for two weeks, unilateral photophobia, and blurred vision in the right eye and tested positive for SARS-CoV-2 reverse transcription–polymerase chain reaction (RT–PCR). The ocular examination revealed bilateral conjunctival hyperemia, accompanied by acute follicular conjunctivitis and acute anterior uveitis in the right eye. The latter was manifested by diffuse, whitish pigmentary immune precipitates on the anterior lens capsule and initial lens opacification, thus explaining the blurred vision [68].

Episcleritis is a common, self-limited inflammation of episclera [69]. Méndez Mangana *et al.* present the case of a 31-year-old patient, who tested positive for COVID-19 infection with no relevant history of ocular pathology, presenting seven days after onset with red eyes, sensation of a foreign body, photophobia without impaired visual acuity. A slightly enlarged epibulbar area with sectoral conjunctival hyperemia on the inferonasal conjunctiva was observed in the left eye, without fluorescein defect, establishing the diagnosis of nodular episcleritis [69].

The retina, being a highly vascularized tissue, is more susceptible to thromboembolic disorders [70]. Although much rarer than outer eye involvement, there were reports of ocular manifestations in the posterior segment, especially in the retina in patients confirmed positive for SARS-CoV-2. A recent report based on the examination of 12 patients diagnosed with COVID-19 showed significant retinal changes. On funduscopic examination, blurring and retinal hemorrhages were observed, suggesting retinal vascular damage. In addition, optical coherence tomography (OCT) examination identified hyperreflective bands, which may indicate inflammation or protein deposits in the retinal layer. These changes are likely related to microangiopathy and hypercoagulability associated with COVID-19, emphasizing the importance of ophthalmological evaluation in patients with severe infection or visual symptoms [71, 72].

Renal manifestations

Acute kidney injury (AKI) is among the complications caused by SARS-CoV-2 infection, being detected in 0.5–7% of cases [73]. Preceding clinical events such as hematuria and proteinuria were observed in approximately 40% of patients [74].

Several factors could contribute to the development of AKI during SARS-CoV-2 infection. Direct viral injury and/or hemodynamic dysregulation of the kidneys could account for the presence of AKI in the context of COVID-19. In addition to the direct effect of SARS-CoV-2 on renal cells, other secondary insults, such as cytokine storms, hypoxia, drug-associated renal toxicity, and secondary infections with other viruses, bacteria or fungi, may contribute to the development of AKI [75].

The apical membrane that lies at the brush border of the proximal tubule shows higher ACE2 expression than lung tissue [76] thus, the virus reaches the arteriolar and glomerular capillaries, later infecting the podocytes, entering the tubular fluid to bind to receptors in the proximal tubules.

Detection of viral traces in urine indicates either a direct contact of coronavirus with the renal tubules or a possible exposure of the renal tubules to the virus [77].

According to the available data, proteinuria and hematuria are commonly observed characteristics in patients with COVID-19 at the time of hospital admission. In addition, CT of the kidneys in patients with COVID-19 showed decreased renal density, indicating the presence of inflammation and edema [78].

Kidneys, being frequently affected by SARS-CoV-2 infection require increased attention in the investigations performed. This virus may not only cause new renal lesions, but also complicate treatment and care, while increasing the mortality rates, especially in people with pre-existing kidney disease [79].

Conclusions

The SARS-CoV-2 infection, responsible for COVID-19, had a significant global impact on public health. SARS-CoV-2 infection mainly affects the respiratory system but also has a significant impact on multiple body systems. Through the ACE2 receptor, the virus enters host cells, triggering a cascade of complex clinical manifestations. In addition to severe respiratory manifestations, such as bilateral pneumonia and ARDS, the virus can also cause neurological manifestations that can range from olfactory and taste dysfunctions to severe conditions such as cerebrovascular events. GI symptoms such as diarrhea, nausea, and vomiting may affect the nutritional status of patients. In the CV system, SARS-CoV-2 contributes to thromboembolic events and myocardial damage. Also, ocular manifestations, although rarer, may indicate the presence of the virus in ocular secretions and may represent a route of transmission of the infection. Renal involvement in the context of SARS-CoV-2 infection is an important aspect of the course of the disease that requires careful monitoring. SARS-CoV-2 is not just a respiratory tropic virus, but a systemic pathogen with complex effects on the whole organism. The neurological, GI, CV, ocular, and renal manifestations emphasize the complexity of this virus, and the lesions caused.

Conflict of interests

The authors declare that they have no conflict of interests.

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