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Clinical and Pathogenic Correlations Between SARS-CoV-2 Infection and Hemolytic Uremic Syndrome in Children

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ABSTRACT

Background: *The present paper examines the correlations between coronavirus disease (COVID-19) and hemolytic uremic syndrome (HUS) from a clinical and pathophysiological point of view.*

Methods: *We describe COVID-19 and HUS by outlining the similarities and differences, detailing each one's pathway into the body, explaining the consequences of the inflammatory response, mainly on multiple organ dysfunction, the foremost complication that can lead to death in both cases. Using reviews from specialized literature and guidelines, we had an approach based on critical interpretive synthesis. Nonetheless, the present article has certain limitations, mainly due to the short period from the emergence of the virus and the ever-increasing body of research that have been shedding light each day.*

Discussion: *Both COVID-19 and HUS require binding to a membrane receptor to trigger the pathophysiological mechanism. Despite the evident difference in tropism, both conditions develop with severe endothelial dysfunction, microangiopathy and important inflammatory response, responsible for MODS. The role of the coagulation pathway is more significant in COVID-19 but less in HUS. Excessive complement activation appears to be a determinant of severe prognosis in both diseases. Regarding COVID-19, children have a milder symptomatology than adults, but in some cases the paediatric inflammatory multisystem syndrome (PIMS) is described.*

Keywords: systemic microangipathy, inflammation, SARS-CoV-2 infection, hemolytic uremic syndrome, children.

INTRODUCTION

The purpose of this paper is to analyze the similarities and differences between hemolytic uremic syndrome and severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection in children from a pathophysiological point of view. The context generated by SARS-CoV-2 pandemic remains a challenge for current medical practice, requiring constant refinement of the system in terms of strategy and prophylaxis. This paper aims to bring a better understanding of the possibility of triggering the infection into the body,

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the interaction between inflammation and coagulation, as well as the role of the inflammatory response emphasizing the effects of cytokine storm based on available current literature and recent body of research.

SARS-CoV-2 is a pathogenic virus that emerged in the region of Wuhan, China, in December 2019, affecting mostly adults, and causing mild to moderate symptoms. However, in certain situations, it presents as acute respiratory distress syndrome (ARDS), especially in older people, with comorbidities, and can subsequently lead to death (1). Coronavirus disease 2019 (COVID-19) infection is potentially problematic due to its rapid interpersonal transmission connected with lack of immunity and unavailability of any specific antiviral treatment (2). SARS-CoV-2 is part of the Coronavirus family: SARS-CoV and MERS-CoV are two other species from the same family, which were acknowledged to be responsible for the epidemics of 2002-2003 and 2012, respectively. Researchers have noticed some similarities between SARS-CoV-2 and the previous two viruses that can have a crucial role in future research, especially in the development of a vaccine (3).

On the other hand, this article describes the hemolytic uremic syndrome (HUS), one of the most common causes of acute renal failure in children beyond the age of five years (4). Hemolytic uremic syndrome is a multisystemic condition characterized by a triad comprising acute renal failure, microangiopathic hemolytic anemia and thrombocytopenia. It is classified into two categories, depending on the association with the Shiga toxin-*Escherichia coli* (STEC), as follows: HUS Typical-STEC (90-95%) and HUS Atypical non-STEC (5-10%) (5).

The passage of the pathogen into the body and the target population

SARS-CoV-2 is an RNA virus, which differs from other viruses by the presence of "spikes" that increase its ability to infect, but nonetheless, it needs a cell to reproduce (1). Therefore, the first step is to bind the S1 subunit from the terminal end of the spikes to the surface molecule of the angiotensin-2 conversion enzyme (ACE-2) (6). As several S1 subunits bind, an envelope will form around the virus (endosome). From this point, the virus can enter the cell using TMPRSS2, a protease that will cleave the S1 to S2 subunits, a mechanism facilitated by low pH or the action of another protease (cathepsin) (7).

Therefore, the virus uses ACE-2 receptors to enter the host cell. ACE-2 is found mainly in the lungs, heart, kidneys and testicles (7). A recent study showed that ACE-2 molecules are found in high concentrations in the oral cavity and tongue, a likely explanation for the fast-oral transmissibility (6). In the healthy lung, ACE-2 is expressed in the alveolar epithelial cells type I and II of the lower poles. When SARS-CoV-2 infects most of the ciliated cells in the alveoli, they will no longer be able to perform their defense physiological activity and will result in a progressive accumulation of cellular debris and fluids in the lungs and ARDS (3).

Children of all ages can be affected by COVID-19. However, they are less affected than adults (1-5% of all confirmed cases) (8). Statistics show that the elderly with comorbidities such as cardiovascular diseases, mainly hypertension, diabetes and chronic kidney disease with a endothelial secondary dysfunction, are the most severely affected people (9). Also, all mentioned pathologies are direct indications of the treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) for the proven beneficial effects (10). There has been speculation that treatment with ACE inhibitors would worsen the disease, but this has not been certified by any observational study (11).

As suggested, myocarditis is the main extrapulmonary complication that makes it difficult to recover from infection (1). It is known that administration of ACE inhibitors after a myocardial infarction is imperative precisely because it leads to a reduction in angiotensin II levels (11). Moreover, another study that analyzed samples from the heart of people who died from SARS-CoV-2 noticed the presence of viral RNA in correlation with low ACE-2 levels (12).

Given the theoretical risks of renin-angiotensin-aldosterone system inhibitors (RAAS inhibitors), several studies have been initiated, which evaluate the clinical outcomes for COVID-19 patients, who are treated with ACE inhibitors (13).

Within HUS, the balance is in favor of certainties, so the presentation will be more concise, without contradictions. In HUS-Typical, the toxin adheres to intestinal cells, causing inflammation, bleeding and ulceration (4). The capacity of STEC to target cells depends on the B subunit that binds to the Gb3 receptor. Penetrating into the cell, the toxin leads to inactivation of protein synthesis, re-

sulting in cell destruction and renal tubular injury. These destructions will trigger a leukocyte-mediated inflammatory response and release of cytokines and chemokines with platelet activation and aggregation (5). In HUS-Atypical, the trigger is a bacterial, viral infection or any other type of endothelial lesion that determines the activation of complement and formation of Gb3 and its subsequent storage in the renal capillaries, followed by activation of the membrane attack complex (4).

Although these two pathologies use distinct receptors to enter the body, HUS and COVID-19 may have more in common beyond their distinctive appearance by triggering pathogenic mechanisms following endothelial cell damage. Hemolytic uremic syndrome is known to be a vasculitis that develops with thrombotic microangiitis, but there are data that suggest that ARDS associated with COVID-19 is the result of extensive endothelial dysfunction that progresses to pulmonary vasculopathy and ultimately triggers excessive inflammatory mechanisms (14).

The body's inflammatory response

Several countries affected by the coronavirus disease (COVID-19) pandemic have recently reported cases of children who were hospitalized in intensive care due to a rare pediatric inflammatory multisystem syndrome. The presenting signs and symptoms are a combination of the ones for Kawasaki disease (KD) and toxic shock syndrome (TSS). A possible temporal association with SARS-COV-2 infection has been hypothesized because some of the children who were tested for SARS-CoV-2 infection were either positive by polymerase chain reaction (PCR) or serology (15).

In a UK study, Elizabeth Whittaker and colleagues at Imperial College London looked at clinical and paraclinical data from 58 hospitalized children who met the PIMP-TS criteria. All subjects had persistent fever, sore throat (10%), headache (26%), abdominal pain (53%), erythematous rash (52%), conjunctival hyperemia (45%), lymphadenopathy (16%), mucosal changes (lips, dry, cracked) (16%). Half of patients (50%) needed hospitalization in intensive care unit, 22% developed acute renal failure, 47% developed shock and required inotropic medication, 43% required mechanical ventilation. In 78% of children there was an association with SARS COV2 infection (PCR SARS-CoV-2 positive in 26% of cases, IgG positive in 87% and negative in 13% of cases) (16).

All patients had marked inflammatory syndrome with C-reactive protein values between 156-338 mg/dL, ferritin values between 369-1280 ug/L, neutrophilia; 68% had elevated levels of troponin and NT-proBNP. Coronary aneurysms were identified in eight patients, of which five belonged to the cardiogenic shock group and only one to the Kawasaki disease group. There were no significant clinical and laboratory differences in patients in whom exposure to SARS-CoV-2 could not be demonstrated (16).

Another study conducted in several pediatric hospitals in the US, on 186 patients, provided more data on the multisystem inflammatory syndrome in children (MIS-C). Unlike Kawasaki disease, however, early reports show that MIS-C predominantly affects adolescents and children older than five years and is associated with more frequent cardiovascular involvement (17). The results of this study can be outlined as follows: the median interval from covid-19 symptoms onset to MIS-C symptoms onset was 25 days; although not sufficient to establish causation, these data suggest that a substantial proportion of patients in this study were infected with SARS-CoV-2 at least one to two weeks before the onset of MIS-C (17).

In most patients (71%) involvement of at least four organ systems was found. The most frequently involved systems and organs were the gastrointestinal (92%), cardiovascular (80%), hematological (76%), cutaneous, mucosal (74%) and respiratory (70%) ones. Cardiovascular involvement was common, with almost half of patients receiving vasopressor or vasoactive support. One in 12 patients had coronary aneurysms and eight (4%) received ECMO support. High levels of BNP and troponin have been detected in 73% and 50% of cases, respectively, while 20% of subjects received invasive mechanical ventilation; also, 92% of patients had at least four positive inflammatory markers (ESR or C-reactive protein, lymphopenia, neutrophilia, elevated ferritin, hypoalbuminemia, elevated ALT, anemia, thrombocytopenia, and elevated D-dimers) (17). The study concludes that MIS-C is part of the spectrum of COVID-19 manifestations, occurring mainly in severe forms of immune-mediated disease, mostly in healthy children and adolescents (17).

The cytokine storm must be mentioned as a systemic inflammatory response due to

SARS-CoV-2 infection, which is especially noteworthy in severely ill patients with COVID-19. Cytokine storm is a general term applied to maladaptive cytokine release in response to infection and other stimuli (18, 19).

Multiple organ dysfunction syndrome (MODS)

Acute respiratory failure and systemic coagulopathy are critical aspects of the morbidity and mortality that characterize SARS-CoV-2 infection. Severe SARS-CoV-2 infection can define a type of microvascular injury syndrome mediated by the activation of complement pathways and associating a procoagulant status (20). Some patients infected with SARS-CoV-2 progress to severe acute respiratory syndrome (SARS), coagulation disorders, metabolic acidosis which responds with difficulty to treatment, and multiorgan dysfunction (MODS); the pathogenic mechanisms are not fully elucidated (21).

As already explained before, the virus uses ACE-2 as a receptor. If the coronavirus, through the viral S glycoprotein, attaches to the ACE-2 receptor in human cells, not only in the lungs but also in other tissues, including kidneys, intestines, heart and brain, it interferes with ACE-2 activity. Thus, the increase in angiotensin II levels could lead to the formation of reactive oxygen species and interference with NOX2 (NADPH oxidase 2) and eNOS (nitric oxide endothelial synthetase), with antioxidant and vasodilating effects, respectively, with additional complement activation.

Thus, the potential loss of self-vasoconstriction and the disorder of pulmonary blood flow through the injured vascular segments would also lead to the increases of shunts and severe hypoxemia (22).

The destruction of pneumocytes determines the release of inflammation mediators (IL-1, IL-6, TNF-α), which at the capillary level, increases vascular permeability and consequently vasodilation, which will lead to the increases of interstitial space and fluid accumulation in the alveoli. Interstitial and alveolar edema occurs, which "washes" the surfactant from the alveoli, so the amount of surfactant decreases, intraalveolar pressure increases, leading to alveolar collapse and hypoxemia (20).

Also, the interleukins released by macrophages attract neutrophils in order to destroy viruses; neutrophils will release oxygen free radicals and proteases, which will lead to destruction of alveolar type 1 and 2 cells, resulting in a further decrease in surfactant levels, decreased gas exchange and increased intraalveolar pressure. All these will lead to processes of lung consolidation (21).

In severe forms, the inflammatory cascade triggers the systemic inflammatory syndrome that can progress to septic shock. Thus, there is a vasodilation with accumulation of fluid in the interstitial space that will lead to decreased circulating volume and peripheral vascular resistance, which will cause a decrease in systemic blood pressure and MODS onset (20).

Severe hemolytic uremic syndrome cases can associate with extrarenal complications such as ARDS, toxic megacolon accompanied by ileus, pancreatitis, central nervous system disorders and multiple organ dysfunction syndrome. Unlike SARS-CoV-2, in severe cases of HUS, the pulmonary edema or pulmonary hemorrhage and ARDS are extremely rare in infants (23).

Some studies show that HUS patients with prolonged thrombocytopenia (more than 14 days) develop MODS. They present a large spectrum of microangiopathy disorders such as thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC) and secondary thrombotic microangiopathy. Due to the incidence of systemic microthrombosis in COVID-19 patients, there are recommendations for the use of anticoagulants (24).

The immune system has an important role in the outcome of the disease. Through primary lung damage, the cytokine storm triggers ARDS, which has multiple consequences. Increased capillary permeability determines a drop in the circulatory volume and systemic vasodilatation. All these changes lead to hypotension and organ hypoperfusion (MODS). ❑

CONCLUSIONS

Both COVID-19 and HUS require binding to a membrane receptor, ACE-2 and Gb3 respectively, to trigger pathophysiological mechanism. Despite the difference in tropism, predominantly renal in HUS and predominantly pulmonary in SARS-CoV-2, both conditions develop with severe endothelial dysfunction, which serves as a precept for the next pathophysiological stage, thrombo-inflammatory, the cytokine storm, responsible for multiorgan manifestations in both conditions.

Furthermore, coagulation activation plays an important role in COVID-19 but less in HUS. Excessive complement activation appears to be a determinant of severe prognosis in both SARS-CoV-2 and HUS-Atypical syndrome, with HUS being observed to activate the alternative pathway as opposed to COVID-19 in which both activation of the alternative and lectin pathway is noted.

Children have a milder symptomatology than adults, but in a minority of cases, the pediatric inflammatory multisystem syndrome (PIMS) is described. The presenting signs and symptoms are a combination of the ones for Kawasaki disease and toxic shock syndrome.

In addition to the contributions reflected in terms of obtained notes, this article has certain limitations. Despite the ever-increasing body of research, large cohort studies are lacking, mainly due to the short period from the emergence of the virus to the present. These are the main limitations and possible source of error of the present article. An increase in the number of patients could provide clearer results, especially where the correlation trend is at the statistical limit. Moreover, some parameters (eg, treatment administered to patients, dose used, analysis of complications) were not explored by this research, but could be considered in future studies. Although some hypotheses have been made, further research is needed to clarify these issues as well as the similarities and differences between the two conditions. ❑

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