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LETTER TO THE EDITOR

Gastrointestinal and hepatic involvement during COVID-19 pandemic: A focus on pediatric population and possible future implications

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Abstract

Since the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide, there is still limited knowledge about this condition and its natural history. Children have been relatively spared during COVID-19 pandemic but a novel syndrome known as multisystem inflammatory syndrome (MIS-C) has emerged, following a SARS-CoV-2 infection in children and adolescents. This syndrome can lead to shock and multiple organ failure requiring intensive care. Although COVID-19 clinical research focuses on respiratory symptoms, extrapulmonary involvement such as gastrointestinal (GI) and hepatic manifestations should also be considered. In fact, GI and hepatic involvement play an important role among the most common presenting symptoms of both pediatric and adult COVID-19 and MIS-C. This involvement can not only be one of the most common presenting clinical features but also one of the sequelae of these syndromes. Abdominal ultrasonography monitoring could be very useful to identify a potential involvement of the GI tract and liver. Moreover, long-term follow-up is needed and would be essential to define the long-term outcomes of these patients.

Key Words: SARS-CoV-2; COVID-19; Multisystem inflammatory syndrome; Gastrointestinal tract; Liver; Ultrasonography

Core Tip: Gastrointestinal and hepatic symptoms are a common clinical feature of the coronavirus disease 2019 (COVID-19). Moreover, a novel syndrome known as multisystem inflammatory syndrome (MIS-C) associated with COVID-19 in children

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and adolescents has emerged. Among the most common presenting symptoms of MIS-C, we found gastrointestinal and hepatic involvement. As gastrointestinal and hepatic involvement might play a major role in the clinical spectrum and possible sequelae of this novel condition, physicians should not underestimate these clinical manifestations. Therefore, abdominal ultrasonography monitoring and long-term follow-up could be useful to evaluate this potential damage and the possible outcome of these patients.

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TO THE EDITOR

We read with great interest the review by Mohamed *et al*[1] about manifestations, mechanisms and management of the gastrointestinal (GI) and hepatic diseases during the coronavirus disease 2019 (COVID-19) pandemic. Although the large majority of concern about COVID-19 and its outcomes is centered on pulmonary manifestations and sequelae, we must be aware that GI and hepatic involvement could play a major role in the clinical spectrum of this novel disease as well as in virus transmission *via* the fecal-oral route. Hence, we agree with the authors' purpose that physicians should not underestimate digestive symptoms during COVID-19. In fact, GI manifestations in COVID-19 patients, including diarrhea, nausea, vomiting, anorexia and abdominal pain are common features of the disease with diarrhea being the most common among these symptoms[2,3].

The pathophysiologic mechanism of GI and hepatic injury during COVID-19 is still debated. Mohamed *et al*[1] reported that GI damage might be due to direct infection of GI cells. We appreciate the great relevance the authors gave to angiotensin-converting enzyme 2 (ACE2) receptors' expression over the small intestine cells, cholangiocytes and hepatocytes and the role it plays in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and in the pathophysiology of both GI and hepatic injury. Also, SARS-CoV-2 can induce cells expressing ACE2 to release inflammatory cytokines leading to a cytokine storm and multiple organ failure[4]. As Mohamed *et al*[1] well reported, SARS-CoV-2 binding to ACE2 receptor can lower the critical receptor level, reducing the absorption of tryptophan on the lumen surface of intestinal epithelial cells. It is known that tryptophan is absorbed on the lumen surface of intestinal epithelial cells *via* the B0AT1/ACE2 transport route inducing the mammalian target of rapamycin which controls the appearance of antimicrobial peptides influencing the components of gut flora. Therefore, the reduced absorption of tryptophan caused by SARS-CoV-2 can ultimately unbalance the gut flora resulting in diarrhea. The changings in the GI flora also stimulate the polarization of T helper 17 cells, and eventually, interleukin 17A induces the recruitment of neutrophils[1]. Moreover, changes in intestinal flora might affect the respiratory tract and *vice versa via* the gut-lung axis, subsequently enhancing the inflammatory and immune-mediated damage in the small intestine.

A study by Pirola and Sookoian[5] demonstrates that gene expression levels for ACE2 are highest in cholangiocytes compared to alveolar type 2 cells, followed in turn by sinusoidal endothelial cells and hepatocytes, thus supporting the possibility that SARS-CoV-2 may cause direct liver injury through a viral cytopathic effect. Nevertheless, GI mucosal damage and unbalance in the gut flora may lead to liver dysfunction through the gut-liver axis.

However, we should not forget that GI tract symptoms and liver injury may also be due to cytokine storm, hypoxic-shock conditions due to acute respiratory distress syndrome and drug-induced injury[6,7].

It is generally accepted that the existence of comorbidities in COVID-19 patients can dramatically increase the risk of poor outcome. Besides, the impact of the COVID-19 pandemic on preexisting GI, liver and pancreatic diseases is still under investigation. We appreciate the importance the authors gave to patients affected by inflammatory bowel diseases (IBD). Actually, these patients are more at risk for infectious diseases

due to the immunosuppressive therapy they undergo. Thus, IBD patients may potentially be more at risk for SARS-CoV-2 infection and severe COVID-19. The prognostic value of the elevation of liver enzymes and indices of cholestasis reflecting hepatic injury and cholangiocellular damage respectively, is still debated. Conversely, pre-existing chronic liver diseases seem to be independent risk factors for poor outcome in COVID-19, and cirrhosis grade has been defined as a predictor of mortality in SARS-CoV-2 infected patients[6].

We are thankful to the authors for their contribution to current literature and we would like to implement the authors' excellent work by reporting our experience with SARS-CoV-2 infection in the Pediatric population.

We would like to emphasize that COVID-19 in children and adolescents may often be asymptomatic or cause only mild symptoms. The most prevalent symptom of COVID-19 in children and adolescents is fever, followed by cough, upper respiratory tract symptoms, diarrhea and nausea/vomiting. In a multinational, multicenter cohort study, 22% of patients had GI symptoms and 7% of those had no respiratory symptoms[8]. Also, neurological manifestations must be considered as they might be a direct result of central nervous system viral invasion or post-infection immuno-mediated disease[9]. Interestingly, in the latter half of April 2020 a previously unknown SARS-CoV-2-related clinical syndrome emerged. Initially this novel entity was named pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by the European Centre for Disease Prevention and Control and then multisystem inflammatory syndrome in children (MIS-C) by the Centers for Disease Control and Prevention (CDC) in the United States and by the World Health Organization. This syndrome can lead to shock and multiple organ failure requiring a Pediatric Intensive Care Unit. Its features resemble those of known entities such as Kawasaki Disease, toxic shock syndrome, and macrophage activation syndrome. The CDC issued a case definition of MIS-C specifying that the patient should be < 21-year-old, have fever, laboratory evidence of inflammation, and evidence of a clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematological, GI, dermatological, or neurological), in the absence of an alternative plausible diagnosis, and evidence of SARS-CoV-2 infection or exposure[10]. It was initially thought that this syndrome was specific of children, but recent reports have shown that it can also occur in adults. In a case series comparing children and adolescents with MIS-C *vs* those with severe COVID-19, MIS-C was distinguished by having a more severe cardiovascular and mucocutaneous involvement and a worse inflammation with a higher neutrophil/Leukocyte ratio, higher c-reactive protein level and lower thrombocytopenia compared to patients with COVID-19[11].

The pathophysiology of this syndrome is under intense investigation but so far it remains unclear. It is believed that this syndrome results from an abnormal immune response to the virus. Interestingly, among the most common presenting symptoms of MIS-C from reports worldwide we found GI involvement, including vomiting, abdominal pain, and/or diarrhea. Moreover, there are reports in literature reporting cases of MIS-C presenting with acute abdomen and pseudo appendicular syndrome with shock, clinical symptoms suggestive of appendicitis, functional intestinal obstruction and ischemic bowel lesions[12,13]. Furthermore, abdominal imaging findings such as hepatomegaly, nephromegaly, gallbladder wall edema, ascites, intestinal inflammation and mesenteric lymphadenopathy are very common[14]. The role of SARS-CoV-2 in some of these clinical presentations seems more likely to be temporal rather than causative but it causes diagnostic and management dilemmas for treating physicians.

Regarding the experience of our Department of Pediatrics, we recently reported the case of a 14-year-old non-obese boy with MIS-C who presented with jaundiced skin, a diffusely painful abdomen and palpable hepatosplenomegaly. He was in a condition of multiorgan failure with a compromised hemodynamic status with reduction of left ventricular ejection fraction and elevated values of alanine aminotransferase, aspartate aminotransferase and indices of cholestasis. Notably, our patient fully recovered from MIS-C, with an excellent cardiac and renal outcome but during the follow-up visit program he was diagnosed with a new onset hepatic steatosis. Therefore, we suggest that hepatic steatosis might be one of the sequelae following SARS-CoV-2 infection, MIS-C or its treatment, mainly due to prolonged use of corticosteroids, probably through an inhibition of mitochondrial fatty acid oxidation[15].

We fully agree with the authors' suggestion that liver function should be monitored during COVID-19, particularly in more severe cases. Furthermore, we think that hepatic involvement after COVID-19 and MIS-C could be underdiagnosed as few patients undergo abdominal ultrasonography monitoring. Diagnosis of hepatic

steatosis is easily accessible through an abdominal ultrasound, which is a low-cost, non-invasive examination. To date, abdominal ultrasound monitoring for these patients is not supported by evidence but we suggest that it could be very useful to identify this potential damage early and evaluate the possible outcome of these patients.

In conclusion, GI and hepatic involvement in COVID-19 and MIS-C should not be underestimated because potential damage could be underdiagnosed. Further studies and long-term follow ups are needed to completely understand the pathophysiology and possible implications that GI and hepatic involvement might have in COVID-19 and MIS-C.

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