Review Article

Gastrointestinal Symptoms and Hepatopancreatic Involvement in COVID-19 Children: A Narrative Review

Sanaz Mehrabani[1*], Maryam Nikpour[1], Leila Moslemi[2]

1. Non-communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
2. Department of Health Reproductive Research Center, Sari Branch, Islamic Azad University, Sari, Iran.

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ABSTRACT

Background: To the best of our knowledge, limited studies explored gastrointestinal (GI) symptoms and hepatopancreatic involvement in children with coronavirus disease 2019 (COVID- 19) infection.

Objectives: This review study aimed to evaluate the GI symptoms and abnormal liver and pancreas function in children with COVID-19 infection.

Methods: In this review study, databases of Scopus, PubMed, Google Scholar, and Web of Science were searched using the relevant keywords of "COVID-19," "children," "gastrointestinal," "liver," and "pancreas." Descriptive and cross-sectional studies were reviewed in the current study, with the main focus on GI symptoms and elevated liver enzymes in children with COVID-19 infection.

Results: Overall, 27 studies from countries of Iran, Spain, Turkey, Italy, and the United States were selected. Although the prevalence of GI symptoms varied in different studies, our review showed that most children with COVID-19 infection experienced GI symptoms. In addition to GI symptoms, there is the possibility of elevated liver enzymes, such as alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and creatine phosphokinase in children with COVID-19 infection.

Conclusions: COVID-19 infection may present various GI, hepatic, and pancreatic manifestations in children. The difference in the prevalence of these symptoms can probably be attributed to the geographical region of the study and the history of the disease.

** Corresponding Author:*
Sanaz Mehrabani, MD.
Address: *Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.*
Tel: *+98 (113) 2346963*
E-mail: *mehrabanisanaz@gmail.com*

1. Introduction

In late 2019, the occurrence of unknown pneumonia in Wuhan, China, and its rapid spread worldwide has become a significant threat to human beings (1). The World Health Organization (WHO) called the cause of this pneumonia coronavirus disease 2019 (COVID-19), and the Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) has proposed to name the novel coronavirus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). WHO announced COVID-19, a global public health threat and international concern that has an incredible and significant effect on the lives of humans. There are more than 87 million confirmed cases and approximately 2 million deaths due to the COVID-19 up to January 10, 2021 (2). Children experience a milder form of the disease than adults (3). The prevalence rate of COVID-19 in children has been reported differently in countries worldwide (4). These rates were 5.8% (5), 1.4% (6), 1.86% (7), and 2.12% (8) in the United States, Spain, China, and Iran, respectively.

It is debatable why not many children catch the disease or have milder symptoms than adults. However, some reasons have been expressed. Angiotensin-converting enzyme 2 is a receptor of the COVID-19 virus (9) and is possibly involved in the pathogenesis of the virus. This receptor is less active in children than in adults. Moreover, in winter, children usually experience a variety of respiratory infections; therefore, there is a higher level of antibodies against COVID-19 in children than in adults (10). Finally, children are cared for at home and are less likely to be exposed to infected patients.

Despite the global spread of the disease, the epidemiology and clinical pattern of COVID-19 are still unknown, especially in children (10), and the risks associated with COVID-19 in children are not exactly determined. Besides, a search of published articles related to COVID-19 indicated that the studies on children are more limited than on adults. Although the gastrointestinal (GI) symptoms have not been recognized in the early stages of the pandemic and are infrequently reported in the literature on infection in patients, it has been reported that a high mean viral load in the nasopharynx is associated with the occurrence of diarrhea in patients with the severe acute respiratory syndrome (11). A better understanding of the ugly and mysterious face of this virus can help control, prevent, diagnose, and optimally treat it by the medical staff. Hence, this review study aimed to clarify the GI, hepatic, and pancreatic manifestations of this virus and its effect on the digestive system.

Gastrointestinal symptoms in children with COVID-19 infection

Although coronavirus in children often presents with respiratory symptoms, it can have GI manifestations such as diarrhea and vomiting, and persistent fecal excretion of the virus raises the possibility of oral-fecal transmission. To the best of our knowledge, there are limited studies on GI symptoms and COVID-19 in children (12). In this review study, databases of Scopus, PubMed, Google Scholar, and Web of Science were searched using relevant keywords of "COVID-19," "children," "gastrointestinal," "liver," and "pancreas." Descriptive and cross-sectional studies were included in the current study, with the main focus on GI symptoms and elevated liver enzymes in children with COVID-19 infection.

Overall, 27 studies involving Iran, Spain, Turkey, Italy, and America were selected. Florian Götzinger et al., in a multicenter cohort study on 582 children from 25 European countries, reported that the frequency of GI symptoms (vomiting and diarrhea) was 22% in COVID-19 children (13).

Five American studies on 800 children with an average age of approximately 12 years indicated that almost all children with COVID-19 experienced at least one GI symptom of vomiting and diarrhea (6, 14-17). In Kainth MK et al.'s study, in addition to diarrhea and vomiting, 40% and 11% of children had anorexia and abdominal pain, respectively (14). Otto WR et al., in a cohort study, suggested that the GI symptoms (vomiting and diarrhea) were generally expressed in 15% of their study group (6).

A multicenter study and 4 studies in different parts of Iran (Tehran, Babol, Qom, and Hamedan, a total of 152 children) suggested that 10% to 60% of these children had GI symptoms such as vomiting, diarrhea, and abdominal pain. Furthermore, anorexia was high in Iranian children with COVID-19 infection (12, 18-21).

The GI symptoms were reported in 10 studies on children with COVID-19 infection (22-30). These studies were performed on 923 children. Chinese children with COVID-19 infection experienced fewer GI symptoms such as vomiting, diarrhea, and abdominal pain (up to 8%).

In Turkey, Yılmaz K et al. (31) and Yayla B et al. (32) examined the clinical signs in 220 and 105 children with COVID-19 infection, respectively. Their study results demon-

strated that the prevalence rate of GI problems was from 2.9% to 7.7%. In Italy, Parri et al. assessed the clinical symptoms of 100 children with COVID-19 infection and reported that the prevalence of vomiting, diarrhea, and abdominal pain was 10%, 9%, and 4%, respectively (33). Presents the GI symptoms in different studies.

Different studies on children indicate different prevalence rates of GI presentations in COVID-19 patients. This difference can probably be attributed to the time and place of the study and the history of the disease in children. Articles from China conducted at the early onset of the COVID-19 pandemic and have shown that GI symptoms are very low or not seen in COVID-19 children. In Iran, in a case series study, the GI symptoms were not reported as clinical symptoms in COVID-19 children (34). However, in other studies performed in later times, the GI symptoms were among the clinical symptoms of the children (12, 35). So far, several types of mutations for this virus have been defined based on Sohrabi et al. (36) and Chen et al.'s studies (37). The variety of symptoms of this disease can be due to the mutations and changes in the behavior of the virus. COVID-19 is a newfound virus, and new features of this virus are found every day (38). The place of the study can also affect the frequency of GI symptoms in COVID-19 children. In countries such as Iran and the United States, the incidence of GI symptoms in children with COVID-19 infection was higher compared to Turkey and Italy. The results of studies indicate that 3.9% to 74% of COVID-19 children had a history of some underlying diseases such as asthma, chronic cardiac disease, cancer, etc.

The duration, severity, outcome, and paraclinical manifestations of COVID-19 infection may be varied based on the clinical pattern of the disease. What needs to be said is that the clinical presentation of COVID-19 is not completely clear. So, the COVID-19 typically presents with fever (85.9%) and respiratory symptoms (60.5%), but there are GI manifestations, including nausea and vomiting, diarrhea, abdominal pain, and lack of appetite, which are less common (39-41). Some studies indicate that in some patients, the only manifestation of the disease may be GI symptoms (42); however, GI manifestations may present earlier than respiratory symptoms (43). On the other hand, the duration from the onset of symptoms to hospitalization is longer in patients with GI manifestation than in those with respiratory symptoms (44). Another study reported the frequency of GI symptoms were from less than 5% to greater than 50% in COVID-19 patients (43).

There is no consistency between the presence of GI presentation and the severity of COVID-19 infection in various studies. Some studies report that the mortality rate is lower, and the course of the disease was milder and slower in patients with digestive symptoms than in those without them (45). Based on a meta-analysis (46), although there was no statistical difference between patients with and without GI symptoms in terms of the severity of COVID-19 disease, 20.5% of patients with GI symptoms had more severe disease than those without GI symptoms (18.2%).

Liver and pancreas function in children with COVID-19 infection

In addition to GI symptoms, some researchers evaluated the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK) in children with COVID-19 infection (12, 18-23, 28, 32). Their tests exhibited that the ALT and AST were increased by at least 17% and at most 40% in these children. In one study, the level of LDH was increased by 17% (20), and approximately 90% of COVID-19 children had an increase in LDH greater than 450 U/L in another study (21). In Mahmoudi et al.'s study, 9% of children with COVID-19 infection had increased CPK levels (19).

Though COVID-19 is mainly considered a respiratory disease, it may also cause liver damage. According to the American College of Gastroenterology, there are abnormal liver enzymes in 20% to 30% of COVID-19 patients (47). Findings of a systematic review and meta-analysis suggest that the pre-existing liver disease was observed in 0.8% to 11% of COVID-19 patients, and 6% to 53% of COVID-19 patients had an increasing level of ALT, AST, and total bilirubin (TB). Also, 6% to 98% of patients had abnormal alkaline phosphatase (ALP) levels during the disease progression. However, the reason for liver transaminase elevation is not just liver involvement (40). The mechanism of liver dysfunction is unclear. Elevated liver function tests in COVID-19 patients might be due to the direct involvement of liver cells from viral infection or drug hepatotoxicity and or immune-mediated inflammation such as cytokine storm and pneumonia-associated hypoxia (47, 48). Of course, it must also be considered that liver dysfunction may occur in patients with pre-existing chronic liver disease (49). Liver dysfunction is more common in COVID-19 patients with severe than the mild disease (48).

In addition, the angiotensin-converting enzyme 2 (ACE2) receptor is highly expressed in the pancreatic

cells; thus, another target of COVID-19 may be the pancreas. Although there is no conclusive information on the prevalence of pancreatitis in COVID-19 children, there is evidence to support this possibility in adults with COVID-19 infection. Liu et al. (50) measured the amount of ACE2 mRNA in the pancreas and concluded that ACE2 mRNA level was higher in the pancreas than lungs. Moreover, they found that in severe cases of COVID-19 infection, there were 17.91% and 16.41% increases in amylase and lipase levels, respectively, indicating pancreatic injury, and nearly 1%-2% of non-severe cases had a pancreatic injury. Another study demonstrated that out of 52 patients with COVID-19, 9 cases (17%) had an abnormal level of amylase or lipase (51). It seems that COVID-19 directly or indirectly causes pancreatic damage. COVID-19 directly has cytopathic effects on pancreatic cells via local SARS-CoV-2 replication and indirectly has systemic effects due to the respiratory failure and immune-mediated cellular responses induced by COVID-19 in infected persons (50, 51). Acute gastrointestinal problems in children, such as diarrhea, vomiting, and abdominal pain, can be part of the manifestation of a pediatric multisystem inflammatory syndrome (3). One of the common symptoms of COVID-19 is myalgia which can present with elevated levels of CPK and LDH, indicating muscle involvement (52).

Studies that specifically examined only GI symptoms and liver enzymes were minimal. Most researchers reported GI symptoms as a part of the clinical symptoms in COVID-19 children.

2. Conclusion

The COVID-19 infection may present various GI, hepatic, and pancreatic symptoms in children. The difference in prevalence can probably be attributed to the geographical region of the study and the history of the previous disease.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Methodology, Writing – original draft, and, and Data collection: Sanaz Mehrabani and Maryam Nikpour; Writing – review & editing: Sanaz Mehrabani, Maryam Nikpour, and Leila Moslemi.

Conflicts of interest

The authors declared no conflict of interest.

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