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## GASTROINTESTINAL TRACT LESION WITH A COVID-19

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### ABSTRACT

Objective of the research: to analyze clinical and laboratory manifestations of COVID-19 with a predominant lesion of the gastrointestinal tract (GIT) in children. It was revealed that incidence of this form of COVID-19 in children is underestimated. Based on the analysis of literature data and original clinical observations, the article describes current ideas about the frequency of detecting the form of COVID-19 with a predominant lesion of the GIT, its clinical and laboratory characteristics, the mechanisms of infectious process development in the digestive organs and approaches to rational laboratory diagnostics. The feasibility of PCR in feces in patients with suspected COVID-19 is confirmed. A description of a clinical case of COVID-19 severe form, which required differential diagnosis with acute bacterial gastroenterocolitis, is presented.

**Key words:** COVID-19, gastroenteritis, children, pandemic, SARS-CoV-2.

### INTRODUCTION

In December 2019, a study of an outbreak of pneumonia in Wuhan (Hubei province, China) identified a new beta-coronavirus - SARSCoV-2 (coronavirus-2, leading to the development of severe acute respiratory syndrome) [1]. The genetic homology of SARS-CoV-2 and previously identified SARS-CoV and MERS-CoV is about 80–85% [2]. SARS-CoV-2 is the 7th identified coronavirus capable of causing disease in humans [2]. In a short time, the spread of this highly contagious pathogen has led to the development of a novel coronavirus infection (COVID-19) pandemic, destabilizing the health care system, economy and all spheres of life of states around the world.

The first reports of a pandemic indicated the predominant involvement of adults and children over 15 years of age in the infectious process [3]. According to currently available data, among patients diagnosed with COVID-19, children accounted for 1 to 5% [4]. Children aged 10–18 years predominated (45.9%), and patients in the first years of life accounted for 26.1% [5]. At the same time, over the period that has passed since the beginning of the pandemic, only a few fatal outcomes of the disease in children have been recorded in world statistics [6]. The further spread of the infection and a significant increase in the total number of cases of COVID-19 in the pediatric population showed that the course of this disease in children has a number of characteristics and is the subject of special attention [7].

The clinical manifestations of COVID-19 are extremely diverse. In the COVID-19 pandemic, doctors focus on the respiratory symptoms of the disease. The most common clinical signs of coronavirus infection in both adults and children include fever, dry cough, manifestations of respiratory failure associated with the development of pneumonia, pulmonary edema or acute respiratory distress syndrome [5, 7]. However, there has been an increasing number of children with COVID-19 who have developed clinical manifestations of gastrointestinal tract (GIT) lesions [8], which indicates the need for a substantive analysis of this group of patients.

The purpose of the work is to analyze the clinical and laboratory manifestations of COVID-19 with a predominant lesion of the gastrointestinal tract in children.

## **MATERIAL AND METHODS**

To solve this problem, a study was carried out, approved by the ethical committee of the Bukhara Regional Multidisciplinary Medical Center for Children's Diseases.

The analysis of publications in PubMed, EMBASE and Web of Science systems in the period from December 2019 to June 2020, highlighting studies documenting the clinical course of the disease with gastrointestinal lesions in patients with a confirmed diagnosis of COVID-19. The following search terms were used: "COVID-19", "SARS-CoV-2", "coronavirus", "SARS-CoV-2 pandemic, epidemic", "outbreak", "diarrhea", "gastrointestinal symptoms", "stool", "feces" without any language restrictions. The main source of information was full-text scientific publications. Additional sources were identified based on an analysis of the bibliography of the included papers.

In addition, clinical cases of COVID-19 among patients of the Department of Intestinal Infections of the Bukhara Regional Multidisciplinary Medical Center for Children's Diseases were analyzed. The clinical manifestations of the disease, the data of laboratory and instrumental studies were assessed. The most informative of them is given as a clinical observation.

## **RESULTS**

Mechanisms of gastrointestinal tract damage in COVID-19.

Coronaviruses are a family of single-stranded enveloped RNA viruses, and their genome has several open reading frames [9]. The first frame contains the largest portion of the viral genome and encodes 16 non-structural proteins, while the others encode structural and accessory proteins. The remaining viral genome is responsible for the expression of four main structural proteins: spike glycoprotein, small envelope protein, template protein, and nucleocapsid protein [9, 10]. The entry of SARS-CoV into the host organism is mediated by the interaction between the spike glycoprotein attached to the virus envelope and the receptor for angiotensin-converting enzyme type 2 (ACE-2) of human cells. According to a number of researchers, the new SARS-CoV-2 has a significantly higher binding affinity for the ACE-2 receptor than its predecessor SARS-CoV2003. At the same time, SARS-CoV-2's peculiarity in comparison with other coronaviruses is its high resistance in the environment. [11].

At the highest concentration, the ACE-2 receptor, which serves as a gateway for SARS-CoV-2, is expressed in lung cells, epithelium of the upper esophagus, and also in enterocytes of the ileum and colon [6].

SARS-CoV-2, acting on the ACE-2 receptors in the gastrointestinal tract, is able to increase the permeability of the intestinal mucosa, which leads to disruption of the absorption of fluid and electrolytes by enterocytes. In addition, it was hypothesized about the possible key role of ACE-2 receptors in the binding of amino acids from the intestinal lumen [12]. Disruption of this receptor function leads to a decrease in the expression of antimicrobial peptides by enterocytes and disruption of the homeostasis of the intestinal microbiota. In experiments on mice, it was shown that viral load can induce enzyme modifications in the intestinal lumen, causing local inflammation of the mucous membrane and the development of secretory diarrhea.

The SARS-CoV-2 virus can directly infect the cells of the organs of the hepatobiliary system, which is confirmed by the detection of increased expression of ACE-2 receptors in cholangiocytes [13]. At the same time, histological examination of liver biopsies in patients with COVID-19 did not reveal the SARS-CoV-2 virus in hepatocytes [14]. Patients with severe liver disease have been shown to have a higher risk of infection and poor outcome from COVID-19 [15, 16]. An increase in the level of transaminases (within 2 times compared with the norm) was noted in 43–57% of patients with COVID-19 [15]. In addition, it was found that the level of transaminases can increase in patients with COVID-19 while taking a number of antiviral drugs (lopinavir and ritonavir) and normalize after stopping treatment [9].

#### Laboratory diagnostics of COVID-19

The COVID-19 pandemic has had a significant impact on the operation of modern diagnostic laboratories, new requirements have arisen for the standardization of routine procedures and the protection of personnel. In case of COVID-19, particular attention is paid to the preanalytical stage of the study. Only the correct, timely sampling of material from the desired anatomical area of the upper respiratory tract, as well as its timely transportation to the diagnostic

laboratory, allow for proper diagnosis of the disease. So, when taking material from a patient on the first day of the disease, the probability of a diagnosis is 94%, and on the 10th day it decreases to 67% [17].

In the laboratory diagnosis of COVID-19, two methods have found the most widespread use: the isolation of viral RNA by real-time reverse transcription PCR (RT-PCR) and the detection of antibodies (AT) to the virus by enzyme-linked immunosorbent assay. RT-PCR today is the "gold" standard for the etiological diagnosis of SARS-CoV-2 infection in the acute period of the infectious process, while the detection of AT serves as an additional tool for clarifying the diagnosis in patients who did not have the opportunity to undergo timely molecular genetic diagnostics. identifying a subclinical form of the disease or when assessing population immunity.

Material for RT-PCR is discharge from the oropharynx and nasopharynx, as well as bronchoalveolar lavage fluid. At the same time, it was shown that SARS-CoV-2 RNA is detected in feces, starting from the 5th day of the disease, and reaches a maximum by the 11th day. At the same time, in a small part of patients, RNA of coronavirus can persist in feces even after the respiratory symptoms disappear, and the results of a corresponding study of samples taken from the respiratory system are negative [8].

#### Clinical manifestations of COVID-19 in children

The incubation period of COVID-19 in children, as in adults, ranges from several days to 14 days, most often about 5-7 days. A short incubation period (72–96 h) is more often observed with a high infectious dose and close contact with a patient with a new coronavirus infection in the family [18]. SARS-CoV-2 is transmitted by airborne droplets and contact transmission. The possibility of implementing the fecal-oral mechanism of transmission of infection is being actively discussed. Children, who have a significant proportion of cases with mild or subclinical forms COVID-19, in epidemiological terms, are of particular importance as a possible source of infection.

According to a meta-analysis by Chinese authors (Z. Wang et al., 2020), based on 49 studies that included 1667 patients with COVID-19 under the age of 18, 83% of children became infected and were ill in family lesions, 19% were asymptomatic carriers [19]. The frequency of severe and extremely severe forms of the disease in children under 1 year of age was 10.6%. In other age groups, the frequency varied from 1.5 to 7.6%, which indicated a high frequency of severe forms of the disease complicated by the development of respiratory failure in children of the first year of life [20]. The high incidence of severe forms of COVID-19 in young children was facilitated by the aggravated premorbid background and concomitant diseases (hydronephrosis, leukemia, intestinal intussusception) [21].

The most common clinical symptoms of COVID-19 in children are cough (48.5%), sore throat (46.2%) and fever (41.5%). Febrile fever is noted in 22.8% of children. Fever above 39.0 C is detected in 9.4% of children [1, 3, 19]. Gastrointestinal symptoms - diarrhea, nausea and vomiting - were found in 7% of

children [8]. A group of researchers (Wu et al., 2020) described the course of COVID-19 in young children, when the disease manifested itself only with diarrhea, bloating and refusal to eat [22]. The main symptoms of a new coronavirus infection with a predominant lesion of the digestive organs in children include fever, lethargy, vomiting, headaches, loose stools, and abdominal pain [8, 22].

It is important to note that the frequency of involvement of the gastrointestinal tract in the infectious process in children with COVID-19 is higher than in adult patients, and is about 3–8% [3, 8]. In a retrospective study, X. Jin et al. in 53 (8.1%) of 651 children, the disease began with watery diarrhea, with an average duration of symptoms of 4 days [23]. In another study, when analyzing a COVID-19 focus in a family, 2 out of 7 patients had diarrhea lasting 3–4 days with a frequency of bowel movements from 5 to 8 episodes per day [18]. The authors noted that the symptoms of gastrointestinal tract lesions disappeared against the background of antiviral therapy.

According to data obtained in the United States by M.L. Holshue et al., The most characteristic symptom of gastrointestinal lesions in patients with COVID-19 was watery diarrhea [24], its duration, according to the authors, ranged from 1 to 4 days. It was noted that a new coronavirus infection with a predominant lesion of the gastrointestinal tract in children is characterized by moderate fever, myalgia, lethargy, headache combined with abdominal pain, nausea, and repeated vomiting.

Respiratory symptoms in COVID-19 with a predominant lesion of the gastrointestinal tract in children appear later, 3–5 days after the onset of gastroenterological symptoms, or do not appear at all [5, 19]. In some patients (12–15%), the leading symptoms were nausea, vomiting, and abdominal pain [19]. When analyzing laboratory data, it was shown that in children, in contrast to adults, changes in the indicators of the clinical blood test against the background of the disease are much less pronounced [25]. Lymphopenia was observed in only 15% (8–22%) of children, in contrast to adults. In biochemical parameters, an increase in hepatic transaminases and markers of systemic inflammation is most often noted. Scatological changes are characterized by moderate disturbances in food digestion, signs of colitis syndrome (detection of leukocytes, mucus in the feces) are much less common.

#### Clinical observation

We present the observation data of the patient U., 12 years old, who was admitted to the Department of Intestinal Infections on June 13, 2020.

Children's Scientific and Clinical Center for Infectious Diseases of the FMBA of Russia on the 4th day of the disease. Due to the epidemiological situation, the boy was hospitalized in a separate box with a swab from the throat and nose for SARS-CoV-2 PCR.

At the time of hospitalization, the patient was diagnosed with the underlying disease: acute gastroenterocolitis of unspecified etiology of moderate severity, complicated by mild exicosis.

The patient complained of vomiting, loose stools, dizziness, weakness, and subfebrile fever. From the anamnesis it was established that he fell ill 4 days before

admission, when the body temperature rose to 39<sup>0</sup> C, from the 2nd day of the illness, loose stools were noted up to 5 times a day, vomiting 4 times a day, periodically abdominal pain without clear localization, headaches. He was observed on an outpatient basis by a pediatrician, received symptomatic drugs (Nurofen), from the 3rd day of illness - orally amoxicillin.

The reason for hospitalization was the prolonged preservation of an increase in body temperature up to 39<sup>0</sup> C, loose stools, the progression of dyspeptic symptoms - increased nausea and abdominal pain.

From the anamnesis it is known that there are 3 people in the family, everyone around is healthy. The early history is not burdened. At 3.5 years old, he suffered from chickenpox. There was no allergic pathology. Preventive vaccinations within the framework of the National Calendar. Attends school regularly. He denies HIV infection, hepatitis, sexually transmitted diseases. There were no injections, transfusions of blood and blood products, as well as injuries and operations during his life. He did not leave St. Petersburg and the Leningrad Region for 6 months.

Upon admission to the infectious diseases hospital, the general condition was assessed as moderate, body temperature 38.70 C. The skin is of normal color, without rash, there are no signs of impaired peripheral microcirculation. Soft tissue turgor is normal. In the pharynx there is moderate hyperemia, the tonsils are loose, without raids. Tongue dry, coated with brown bloom at the base. Peripheral lymph nodes are not enlarged. Pulse 94 beats per minute. Blood pressure 110/68 mm Hg. Art. The boundaries of relative cardiac dullness are not expanded. Heart sounds are clear, rhythmic, without pathological murmurs. Respiration rate 19 per minute. Percussion over the pulmonary fields pulmonary sound. Vesicular breathing is carried out evenly over the entire surface of the lungs, wheezing is not heard. The abdomen is symmetrical, soft, with deep palpation moderately painful along the colon. Symptoms of peritoneal irritation are negative. The liver and spleen are not enlarged. Diuresis is sufficient, no dysuria. The stool on the eve of admission in the morning was liquid without pathological impurities.

On the basis of complaints, anamnesis data of the disease, severe general intoxication syndrome, local intestinal syndrome in the admission department, a preliminary clinical diagnosis was established: acute gastroenterocolitis, of moderate severity, complicated by mild exsiccosis. From admission, therapy was prescribed: oral rehydration, dietary correction; etiotropic (parenteral cephalosporins) and pathogenetic therapy (enterosorbent, probiotic), symptomatic agents (antispasmodic).

In laboratory parameters, attention was drawn to a pronounced increase in the level of CRP 532 mg / l, in the hemogram - lymphopenia and pronounced neutrophilia with a stab shift.

The coprogram revealed signs of colitis (leukocytes up to 10 in the field of view). Considering prolonged fever, loose stools, abdominal pain, laboratory data (signs of systemic inflammation according to hemogram and biochemical blood analysis, inflammatory changes in the coprogram), the condition was regarded as

an acute bacterial intestinal infection, acute enterocolitis. The therapy was adjusted: a broad-spectrum antibacterial drug (Ceftriaxone) was added to the therapy. At the same time, instrumental examination was carried out to exclude extraintestinal foci of bacterial infection: chest x-ray, ultrasound (ultrasound) of the kidneys, general urinalysis, and examination by an otorhinolaryngologist.

According to the results of laboratory tests: PCR of feces for pathogens of the intestinal group (microorganisms of the genus *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., Adenoviruses of group F, rotaviruses of group A, noroviruses of the 2nd genotype and astroviruses, diarrheogenicescherichias), as well as *Yersuberculosispseudotis* and *Yersinia enterocolitica* were not identified. Microbiological examination of feces of pathogenic microorganisms of the family Enterobacteriaceae was not found. Antibodies to *Y. pseudotuberculosis* and *Y. enterocolitica* were not detected by ELISA. RNGA with salmonella-dysentery antigen is negative.

Ultrasound of the abdominal organs: free fluid in the abdominal cavity was not detected; intestinal pneumatization is increased; para-aortic and intra-abdominal lymph nodes are not visualized; deformation of the gallbladder.

Ultrasound of the kidneys: no pathology.

Chest X-ray: no acute infiltrative changes.

Against the background of the ongoing complex therapy, the patient's condition remained stable without clear dynamics. There were persistent abdominal pains, severe lethargy, persistent febrile fever. In the biochemical analysis of blood on the 3rd day of treatment, a decrease in the level of CRP to 165.2 mg / l was noted.

On the 3rd day from the date of admission, a positive test result for SARS-CoV-2 was obtained. In connection with the probable course of COVID-19, for further treatment, the patient was transferred to a specialized department, where, during further examination, the diagnosis of COVID-19 with a predominant gastrointestinal lesion was confirmed. Worth also

It should be noted that in the course of further examination, a spiral computed tomography of the chest organs was performed, which did not reveal signs of a respiratory infection. A repeated attempt was made to establish a possible combination of COVID-19 with another bacterial pathogen (bacterial inoculation and fecal PCR were carried out), which did not lead to the identification of pathogenic microorganisms. Against the background of the ongoing complex therapy, an improvement was noted: normalization of body temperature (on the 7th day of inpatient treatment), the nature and frequency of stools (on the 9th day of inpatient treatment). 42 days after the onset of symptoms of the disease, the patient independently turned to a private laboratory to establish the presence of antibodies to SARSCoV-2, where a high titer of IgG to SARS-CoV-2 was detected.

This example illustrates the difficulties that doctors face when making a preliminary diagnosis in patients with gastrointestinal tract damage with COVID-19. Colitis syndrome in the coprogram, the presence of positive dynamics against the background of antibiotic therapy. At the same time, attention was drawn to the

discrepancy between the normal total level of leukocytes and a pronounced increase in CRP, as well as severe lymphopenia, which are not characteristic of bacterial intestinal infections, which, along with epidemiological alertness during a pandemic and a negative result of fecal examination for a wide range of pathogens of intestinal infections allowed to suspect COVID-19.

### **DISCUSSION**

In the current COVID-19 pandemic, the focus of both children and adults is on the respiratory symptoms of the disease. Nevertheless, the number of patients with the development of gastrointestinal tract lesions in COVID-19 is significant and should not be underestimated.

Depending on the diagnostic criteria used in the studies, the proportion of children with COVID-19 with diarrhea ranges from 2 to 50% of cases [8, 19]. It cannot be ruled out that the available data underestimate the incidence of gastrointestinal lesions in COVID-19. At the same time, taking these symptoms into account as probable manifestations of COVID-19 is extremely important for assessing the epidemic situation and is fundamental for timely diagnosis during an increase in the incidence of COVID-19.

When conducting further research, it is necessary to apply clear criteria for the presence of diarrheal syndrome and characterize its severity. The development of diarrhea in a number of patients in the absence of respiratory symptoms, as shown in the above case study, can lead to an underestimation of COVID-19 cases, since further research may not be carried out in patients with mild symptoms.

Another limitation is related to the information content of diagnostics. The analysis of samples obtained from the respiratory tract does not detect all cases of infection. A recent study used a mathematical model to determine the dynamics of COVID-19 infection in China. It turned out that at least 86% of cases of infection were not registered and that patients with "missed" cases of the disease subsequently led to infection of the majority (79%) of patients with proven infection with COVID-19 [26].

Detection of SARS-CoV-2 RNA in feces and in histological samples from the gastrointestinal tract, long-term persistence of the virus in feces in comparison with nasopharyngeal smears indicate that fecal-oral transmission plays an important role in the spread of the disease [8]. Moreover, this phenomenon confirms the advisability of performing PCR in feces in patients with suspected COVID-19.

### **CONCLUSIONS**

Thus, the presence of diarrhea in children during the COVID-19 pandemic requires the exclusion of infection caused by SARS-CoV-2 by adequate laboratory diagnostic methods. The incidence of diarrhea in children with COVID-19 is currently underestimated. Further research is needed to assess the role of gastrointestinal tract damage in the COVID-19 clinic, to compare the sensitivity of fecal and nasopharyngeal discharge methods, and to assess the prognostic value of gastrointestinal tract damage in COVID-19 in children.

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