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Gastrointestinal symptoms of COVID-19 in children

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ABSTRACT

Introduction: The COVID-19 pandemic progresses. The clinical manifestation of the disease and the severity of its course vary significantly. There are considerable differences between symptoms of SARS-CoV-2 infection in the child and adult populations. The gastrointestinal (GI) symptoms are an essential element in understanding the pathophysiology of the disease and in drawing conclusions concerning the diagnostic, therapeutic, and epidemiological management of COVID-19. The aim of the study was to characterize the gastroenterological symptoms of COVID-19 in the paediatric population and to find differences in the course of the disease between paediatric patients with and without GI symptoms of COVID-19.

Material and methods: We report the clinical characteristics of 321 children with COVID-19 (age 0–215 months) hospitalized between March 2020 and April 2021. The following division was used when processing the data: the first wave of cases in Poland lasted from the beginning of the pandemic to June 2020, the 2nd wave September–November 2020, and the 3rd wave February–May 2021. We specifically compared the differences between patients with and without GI symptoms.

Results: Among all included patients, 95 (29.5%) had GI symptoms – the most common included abdominal pain (15.27%) and diarrhoea (14%). Approximately 3% of patients with GI symptoms required surgical intervention. As the pandemic progressed, GI symptoms were reported with increasing frequency – during the first wave 9%, the second wave 25%, and the third wave 38%. Patients with GI symptoms had more frequent and statistically significantly higher inflammatory parameters. During treatment, GI patients more often required the administration of antibiotics. The most common abdominal ultrasound abnormalities were liver enlargement, a slight amount of free fluid in the peritoneal cavity, and moderately enlarged individual lymph nodes.

Conclusions: Gastrointestinal symptoms form an image of COVID-19, which is a possible prognostic risk factor for severe course of the disease. Gastrointestinal symptoms should be treated as a possible isolated image of COVID-19.

KEY WORDS:

children, gastrointestinal symptoms, COVID-19, inflammatory parameters.

INTRODUCTION

The COVID-19 pandemic has been spreading continuously for 2 years. At the time of writing, 0.5 billion SARS-CoV-2 infections have been reported, and approximately 6 million people have died of the disease [1]. In the general population, the most common symptoms of the disease are as follows: fever (58.66%), cough (54.52%), dyspnoea (30.82%), malaise (29.75%), fatigue (28.16%), and sputum secretion (25.33%) [2]. The clinical

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course of COVID-19 in children is usually asymptomatic or mild [3, 4]. In symptomatic disease, they present cough (48%), fever (47%), and sore throat (28.6%) [5]. In adults, the most common gastrointestinal (GI) symptoms are anorexia (10.2%), diarrhoea (8.4%), and nausea (5.7%). Nearly a quarter of children with COVID-19 develop GI symptoms (22.8%). The most frequently reported GI symptom was diarrhoea (12.4%), followed by vomiting (10.3%) and abdominal pain (5.4%) [6]. Compared to influenza, GI symptoms in COVID-19 are twice as common (10.3% in COVID-19 versus 4.5% in influenza) [7]. Several mechanisms that may be responsible for this phenomenon have been found. The receptor for the virus is angiotensin-converting enzyme 2 (ACE2) [8]. The entry of the virus causes internalization of ACE2, thus reducing the availability of the enzyme, which impacts vasoconstriction and pro-inflammatory and profibrotic pathway induction [9, 10]. Angiotensin-converting enzyme 2 is expressed in lung alveolar type 2 cells and in the oesophagus epithelial cells, the absorptive enterocytes of the ileum and colon, the liver, and many other tissues [11–14]. Some scientists present the possibility of the so-called gut-lung axis, which can be the communication pathway of both systems through pro-inflammatory cytokines, migrating cells of the immune system, and the mutual influence on the microbiota [15]. Furthermore, a decreased expression of ACE2 on the surface of the enterocytes reduces the absorption of tryptophan, which increases the pro-apoptotic effect of mTOR kinase activity, disturbs the GI motility via decreased serotonin synthesis, and modifies intestinal microbiota composition [16]. The presence of symptoms other than respiratory among adults is associated with a severe course of COVID-19. Adult and paediatric patients with GI symptoms have severe, critical illness and fatal outcomes more often than those without this type of manifestation [6, 17, 18]. The aim of the study was to characterize the GI symptoms of COVID-19 in the paediatric population and to find differences in the course of the disease between paediatric patients with and without GI symptoms of COVID-19.

MATERIAL AND METHODS

We conducted a retrospective chart review of 321 children with COVID-19 (age 0–215 months) hospitalized between March 2020 and April 2021 in the Department of Infectious Diseases and Child Neurology (Poznan University of Medical Sciences). SARS-CoV-2 infection was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) tests (various analysers) from nasopharyngeal swabs. At the time of admission to the hospital, in accordance with national guidelines, all patients with any sign of infection (e.g. fever) were tested for SARS-CoV-2, including those without symptoms of respiratory tract infection. The study included 321 children: 169 boys and 152 girls. The median age of the patients was 54 months, and the interquartile range (IQR) was 15–149 months. There were no people with GI diseases (e.g. with inflammatory bowel diseases) in the study group. The definition of a patient "with GI symptoms" required that they have at least one of the following symptoms: nausea, vomiting, diarrhoea, blood in the stool, mucus in the stool, or abdominal pain. The following division was used when processing the data: the first wave of cases in Poland lasted from the beginning of the pandemic to June 2020, the 2nd wave September–November 2020, and the 3rd wave February–May 2021. Laboratory testing involved complete blood count, C-reactive protein, procalcitonin (PCT), clinical chemistry parameters, fibrinogen level, international normalised ratio, and D-dimer. Patients were treated according to the current recommendations. Treatment was based on the following: remdesivir, convalescent plasma, steroids, and antibiotics (3rd-generation cephalosporins, azithromycin), depending on indications. The data collected during the examination were subjected to statistical analysis. The normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test. Data were presented as median value and 25–75 IQR. Due to the distribution other than normal, comparisons of continuous variables between 2 different groups were performed using the Mann-Whitney U test and χ^2 test. A p-value below 0.05 was considered statistically significant. The percentile grids were based on the results of the OLA and OLAF studies for the Polish population and the World Health Organization percentile grids. PQ Stat v1.6.6 software was used for statistical analysis. The Ethics Committee at Poznan University of Medical Sciences approved the study (No. 2865/20).

RESULTS

Among 321 children with COVID-19, 95 (29.5%) had GI symptoms. The groups of patients (with and without GI symptoms) did not differ in demographic and anthropomorphic parameters (Table 1). In the group with GI symptoms, the time from onset of symptoms to hospital admission was significantly longer (mean 3.39 to 2.61 days, $p = 0.032$) (Table 1). The most common GI symptoms in children were abdominal pain (15.3% of all patients, $n = 49$) and diarrhoea (14%, $n = 45$). Nausea and vomiting were present in 11.5% ($n = 37$) of patients. The least frequent were the presence of blood (2.5%, $n = 4$) or mucus in the stool (0.6%, $n = 1$). Because of the acute abdomen symptoms, approximately 3% ($n = 10$) of patients required surgical intervention (the final diagnosis was acute appendicitis). The characteristics of symptoms other than GI in children did not differ significantly between the groups, apart from an increased incidence of pharyngitis, which was reported in the group of patients with GI symptoms (Table 2).

Gastrointestinal symptoms were reported with increasing frequency as the pandemic progressed. During

TABLE 1. Epidemiological and clinical characteristics of COVID-19 children with and without gastrointestinal symptoms

Parameters		All patients	Patients without GI symptoms	Patients with GI symptoms	*p*-value
Age (months)		*N* = 321 Mean ±SD: 78.99 ±71.70 Median: 54 IQR (25–75): 15–149	*n* = 226 Mean ±SD: 83.67 ±74.99 Median: 52 IQR (25–75): 15–164.25	*n* = 95 Mean ±SD: 67.87 ±62.14 Median: 56 IQR (25–75): 14.5–118.75	0.14
Age group distribution, *n* (%)	0–12 months	70 (21.81)	48 (21.24)	22 (23.16)	
	1–3 years old	66 (20.56)	45 (19.91)	21 (22.11)	
	3–6 years old	49 (15.27)	33 (14.60)	16 (16.84)	
	6–12 years old	56 (17.45)	35 (15.49)	21 (22.11)	
	12–18 years old	80 (24.92)	65 (28.77)	15 (15.79)	
Sex, *n* (%)		M: 169 (52.65) F: 152 (47.352)	M: 119 (52.66) F: 107 (47.34)	M: 50 (52.63) F: 45 (47.37)	0.99
Mass percentile		*N* = 155 Mean ±SD: 60.47 ±31.35 Median: 67 IQR (25–75): 35–89	*n* = 97 Mean ±SD: 60.85 ±32.45 Median: 70 IQR (25–75): 33–91	*n* = 58 Mean ±SD: 59.83 ±29.7 Median: 66 IQR (25–75): 37–85	0.67
Growth percentile		*N* = 75 Mean ±SD: 60.30 ±34.25 Median: 67 IQR (25–75): 32–92	*n* = 50 Mean ±SD: 60.12 ±32.28 Median: 66 IQR (25–75): 36,5–88	*n* = 25 Mean ±SD: 60.68 ±38.59 Median: 74 IQR (25–75): 24–96	0.67
BMI percentile		*N* = 75 Mean ±SD: 53.49 ±32.29 Median: 54 IQR (25–75): 26.5–84.5	*n* = 50 Mean ±SD: 53.72 ±33.57 Median: 55 IQR (25–75): 27.75–87	*n* = 25 Mean ±SD: 53.04 ±30.24 Median: 53 IQR (25–75): 26–83	0.81
Days from illness onset to admission		*N* = 306 Mean ±SD: 2.85 ±3.27 Median: 2 IQR (25–75): 1–4	*n* = 213 Mean ±SD: 2.61 ±3.18 Median: 1 IQR (25–75): 1–3	*n* = 93 Mean ±SD: 3.39 ±3.42 Median: 2 IQR (25–75): 1–4	0.032
Presence of chronic diseases, *n* (%)		107 (33.648)	81 (36.32)	26 (27.37)	0.12

BMI – body mass index, GI – gastrointestinal, IQR – interquartile range
[1]congenital heart defects; genetic diseases (e.g. trisomy 21); bronchopulmonary dysplasia etc.

TABLE 2. Characteristics of COVID-19 symptoms in the study group (division into patients with and without gastrointestinal symptoms)

Symptoms	*N* patients	Patients without GI symptoms	Patients with GI symptoms	*p*-value
Fever, *n* (%) Low-grade fever, *n* (%)	*N* = 321 149 (46.417) 27 (8.411)	*n* = 226 101 (44.69) 20 (8.849)	*n* = 95 48 (50.526) 7 (7.368)	0.62
Duration of the fever (days)	*N* =172 Mean ±SD: 3.07 ±7.82 Median: 2	*n* = 120 Mean ±SD: 2.72 ±2.34 Median: 2	*n* = 52 Mean ±SD: 3.89 ±8.01 Median: 2	0.47
Cough, *n* (%)	112 (35.11)	82 (36.61)	30 (31.58)	0.31
Chest pain, *n* (%)	13 (4.075)	11 (4.93)	2 (2.083)	0.24
Pharyngitis, *n* (%)	74 (23.418)	44 (19.91)	30 (21.58)	0.025
Pneumonia, *n* (%)	43 (13.57)	31 (14.03)	12 (12.5)	0.72

GI – gastrointestinal

the first wave, these symptoms were visible in 9% of patients, during the 2nd wave in 25%, and during the 3rd wave in 38% (Figure 1). Patients with GI symptoms had statistically significantly higher inflammatory parameters: white blood cells (WBC), C-reactive protein (CRP), and PCT compared to the group without GI symptoms (Table 3). Moreover, the frequency of elevated parameters (CRP and PCT) were higher in this group. Patients with GI

symptoms more often required the administration of antibiotics (ceftriaxone) than patients without GI symptoms (34.38% vs. 20.89%, respectively) ($p = 0.01$). In contrast, intravenous steroid therapy, used for dyspnoea, was more often required by patients without GI symptoms (25.47% vs. 8.62%, $p = 0.009$).

The most common abdominal ultrasound abnormalities among patients with GI symptoms were liver enlargement, a slight amount of free fluid in the peritoneal cavity, and moderately enlarged individual lymph nodes. Several patients had signs of intussusception. Inflammatory changes in the intestinal wall were rarely visualized and restricted. Statistical analysis was limited considering the small research sample, large age variation, and various accompanying diseases.

DISCUSSION

In the presented study 29.5% of patients had GI symptoms – slightly more than reported in the paediatric COVID-19 meta-analysis (22.8%). Abdominal pain was much more frequently identified in the study group (15.3% vs. ~5.5%) [6]. The reasons for these results may be a more severe course of disease in the research group (the study included only hospitalized patients), antibiotic therapy side effects [19], or hospitalization-related stress [20]. Moreover, abdominal pain during COVID-19 may be an underestimated symptom among outpatient patients due to underdiagnosis of SARS-CoV-2 infections in people who do not present the red flag symptoms (fever, dyspnoea, cough). The time from the first signs of

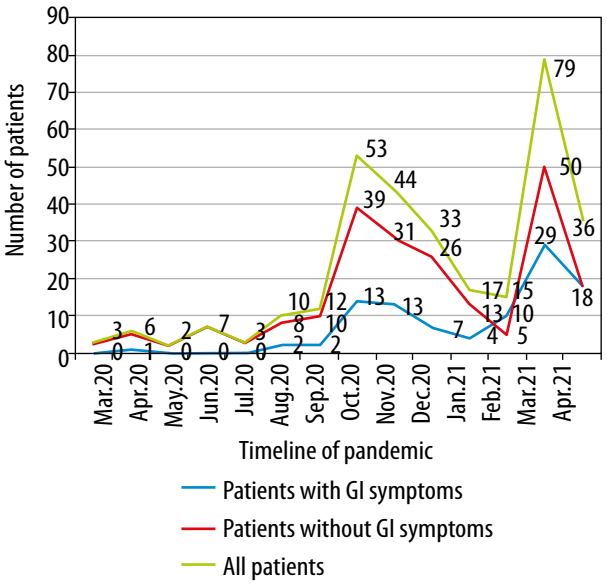

FIGURE 1. Number of patients with and without gastrointestinal symptoms during the pandemic

GI – gastrointestinal

COVID-19 to hospitalization was statistically longer in patients with GI symptoms. It has been reported that presenting isolated GI symptoms can delay the diagnosis and worsen outcomes [21]. In the research group, as in other reports, acute abdomen appeared as a solitary symptom of SARS-CoV-2 infection [22]. About 3% of our patients required surgical intervention for this reason. Some of them were diagnosed with the virus during routine tests performed in the surgical ward. Fever appears to be less common in relatively young patients diagnosed with

TABLE 3. Characteristics of COVID-19 laboratory parameters in the study group (division into patients with and without gastrointestinal symptoms)

Laboratory parameters	All patients $N = 321$ median ±SD (range)	Patients without GI symptoms $n = 226$ median ±SD (range)	Patients with GI symptoms $n = 95$ median ±SD (range)	*p*-value
Haemoglobin [g/dl]	12.4 ±1.65 (7.3–18.1)	12.5 ±1.61 (7.6–17.3)	12.4 ±1.74 (7.3–18.1)	0.36
Platelet count [10^3/µl]	271.5 ±116.63 (2–751)	276 ±116.54 (2–751)	267 ±117.44 (5–717)	0.80
Red blood cell count [10^6/µl]	4.58 ±0.65 (2.53–10)	4.6 ±0.67 (3.1–10)	4.56 ±0.62 (2.53–6.07)	0.28
White blood cell [10^3/µl]	7.79 ±4.66 (0.61–29.07	7.52 ±4.40 (0.61–29.07)	8.73 ±5.10 (1.06– 26.62)	0.04
Neutrophils (%)	49.6 ±22.3 (1.13–90.9)	49.2 ±20.79 (1.13–90.9)	53.95 ±25.26 (2.3–86.5)	0.47
Lymphocytes (%)	36.35 ±20.80 (6.2–87.6)	37.35±19.08 (7–85.3)	33.15 ±24.11 (6.2–87.6)	0.36
CRP [mg/dl]	0.21 ±3.4 (0–28.2)	0.2 ±1.7 (0–13.96)	0.35 ±5.49 (0–28.2)	0.001
Patients with elevated CRP (> 0.5 mg/dl), *n* (%)	107 (33.44)	63 (28)	44 (46.32)	0.0016
PCT [ng/ml]	0.04 ±5.36 (0.01–83.35)	0.03 ±0.66 (0.01–7.41)	0.06 ±9.34 (0.01–83.35)	0.0001
Patients with elevated PCT (> 0.05 ng/ml), *n* (%)	125 (46.47)	69 (37.91)	56 (64.37)	0.00005
AST [U/l]	31 ±88.82 (10–1505)	31 ±19.25 (10–210)	31 ±153.98 (12–1505)	0.62
ALT [U/l]	17 ±68.08 (5–1105)	17 ±22.43 (5–259)	16±115.64 (5–1105)	0.85
Creatinine [mg/dl]	0.33 ±1.06 (0–17)	0.33 ±1.22 (0–17)	0.32 ±0.58 (0–5.63)	0.85

ALT – alanine transaminase, AST – aspartate transaminase, CRP – C-reactive protein, GI – gastrointestinal, PCT – procalcitonin

mild to moderate COVID-19. Data suggest that body temperature or respiratory symptoms alone may be a poor indicator of SARS-CoV-2 infection in children [23]. Abdominal symptoms (including acute abdomen) should be treated equally with common infection symptoms such as fever or cough as possible symptoms of COVID-19.

Vomiting is a common symptom of infection in the paediatric population (11.5% in our study). According to meta-analyses, they appear in 8–10% of paediatric patients with COVID-19 [5, 6]. We observed increased incidence of pharyngitis in the group of patients with GI symptoms ($p = 0.02$). Vomiting can be a consequence, a cause, and a symptom accompanying pharyngitis. Therefore, an unequivocal assessment of the correlation is difficult. Some authors suggest the existence of specific mechanisms inducing vomiting in the course of COVID-19, especially by emetic mediators released from the intestinal enteroendocrine cells damaged during inflammation [24].

In patients with COVID-19 with pharyngitis during swallowing, the higher viral load from the upper respiratory tract may move further into the digestive system with swallowed mucous [16], subsequently involving the lower parts of the digestive system.

Diarrhoea among our patients occurred with a similar frequency as reported in the literature (14/12.4%) [6]. It is important to consider faecal-oral transmission and the time of virus excretion in the faeces when planning pandemic control measures [13]. Blood or mucus in the stools were rare and reported only in a few patients.

As the pandemic progressed, GI symptoms among our patients were reported with increasing frequency. This may be due to a broader diagnosis towards SARS-CoV-2, the affinity of the new variant virus, and the change in the course of the disease. However, published data show that the Delta variant that appeared during the 3rd wave period was not associated with an increased frequency of GI symptoms [25].

Patients with GI symptoms had statistically significantly higher inflammatory parameters (WBC, CRP, and PCT) than those without GI symptoms. They more often required the administration of antibiotics (ceftriaxone) during treatment. Similar observations were described by other authors: the correlation between inflammatory parameters (PCT and CRP) and disease severity [26], as well as the occurrence of GI symptoms and the severe course of COVID-19 in children [18].

However, among our patients with pneumonia GI symptoms were not more frequent than in the entire study group, which does not confirm the existence of the gut-lung axis in practice. We do not exclude such a possibility. The network of connections between the various foci of virus multiplication is dense – through continuity, pro-inflammatory cytokines, migrating cells of the immune system, and the mutual influence on the microbiota [15].

CONCLUSIONS

Gastrointestinal symptoms should be treated as a possible isolated image of COVID-19 and a possible prognostic risk factor for the severe course of the disease. Patients with abdominal symptoms present high inflammatory parameters. Studies on the pathophysiology of SARS-CoV-2 are needed to discover connections between apparently distant organs, between the microbiota of the digestive system and the organism, and to analyse the network of immune interactions exacerbating the inflammatory process during COVID-19.

DISCLOSURE

The authors declare no conflicts of interest.

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