

TOPICAL ISSUE

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FEATURES OF GASTROINTESTINAL DISORDERS IN CHILDREN WITH MULTISYSTEM INFLAMMATORY SYNDROME ASSOCIATED WITH COVID-19

Resume. Gastrointestinal tract damage is a part of the course of multisystem inflammatory syndrome in children (MVS-D) associated with the new COVID-19 coronavirus infection. According to the results of a retrospective study, gastrointestinal tract damage was detected in 77% of patients with MVS-D and is represented by signs such as abdominal pain, vomiting, diarrhea and peritoneal symptoms. In children with gastrointestinal tract lesions, significant differences were noted in the frequency of occurrence of the following signs: hepatomegaly, splenomegaly, hypotension/shock, as well as conjunctivitis and facial swelling. Among laboratory abnormalities, hypoalbuminemia is more characteristic, but the level of CRP and troponin is higher. The article shows that gastrointestinal tract damage is an important early predictor of the severity of MVS-D.

Keywords: multisystem inflammatory syndrome, gastrointestinal tract lesion, hepatomegaly, splenomegaly, Russia.

Introduction. According to systematic reviews, cases of COVID-19 in children were observed relatively less frequently, and, mostly, had a lighter course [14, 15, 4, 22]. The incidence in children is estimated from 1-5% to 19% of all COVID-19 cases. [14, 3]. For the first time, the suspicion of a possible link between COVID-19 and Kawasaki disease (KD) was put forward by Jones et al [12], who reported a case of Kawasaki disease in a 6-month-old girl with positive PCR result on SARS-CoV-2. Also among the first to describe this problem were groups of researchers from Italy [19] and France [17]. However, this condition occurs in older children than KD, and is also often manifested with gastrointestinal symptoms (diarrhea, abdominal pain, vomiting) and heart disorders (myocarditis, pericarditis), which often lead to myocardial damage and shock, while these clinical manifestations are less common in KD [13]. This phenomenon was later called multisystem inflammatory syndrome in children (MIS-C). The incidence of MIS-C is 1:4000 children who had COVID-19 [8]. One of the most frequent early manifestations and features that help to distinguish MIS-C from KD is the involvement of gastrointestinal tract in the pathological process, manifested by abdominal pain, diarrhea, nausea and vomiting, and in some cases with mesenteric lymphadenitis.

The aim of the study: To analyze the main clinical and laboratory characteristics of the disease course and to determine the factors associated with the gastrointestinal involvement in MIS-C.

Materials and methods: In the retrospective study were included 162 patients (96 boys, 66 girls) aged from 4 months to 17 years (median 8.2 years) with a diagnosis of "multisystem inflammatory syndrome associated with COVID-19 in children" who were on inpatient treatment in pediatric clinics of Saint Petersburg, Irkutsk, Yakutsk, and Kaliningrad. The inclusion criteria met the criteria of the World Health Organization (WHO) for the definition of MIS-C. Inclusion criteria (all items must be present):

1. Age from 0 to 18 years.
2. Fever for ≥ 3 days.
3. Clinical signs of a multisystem disorders (at least 2 of the following):
 - Rash, bilateral non-purulent conjunctivitis or signs of inflammation of the skin and mucous membranes (oral cavity, hands or feet).
 - Hypotension or shock.
 - Cardiac dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiographic data or elevated troponin/BNP).
 - Signs of coagulopathy (prolonged PT or PTT; elevated D-dimer).
 - Acute gastrointestinal symptoms

(diarrhea, vomiting, or abdominal pain).

4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin).

5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes.

6. Signs of previous COVID-19: Positive PCR of SARS-CoV-2 / Positive serology / Positive antigen test / Contact with a person with confirmed COVID-19.

The fact of previous COVID-19 infection in patients was confirmed by at least one of the following methods: a positive result of PCR with reverse transcription (13%), the presence of antibodies of classes IgM (40.3%) or IgG (97.4%) to SARS-CoV-2, contact with a person with confirmed COVID-19 (65.6%).

The frequency of clinical signs and the severity of laboratory changes in patients with MIS-C were evaluated. To conduct a comparative analysis, patients with MIS-C were divided into two groups: group 1 - with gastrointestinal disorders (n=125, 77.2%) and group 2 - without signs of gastrointestinal disorders (n=37, 22.8%).

Statistical analysis was performed with the software STATISTICA, version 10.0 (StatSoft Inc., Tulsa, OK, USA). The description of quantitative indicators is carried out with the indication of the median (25th; 75th percentiles). Comparison

of qualitative indicators was carried out using the Pearson criterion χ^2 . Comparison of quantitative indicators was carried out using the Mann-Whitney criterion. For quantitative variables, cut-off values were calculated using AUC-ROC analysis (AUC – area under the curve – "area under the curve") with the determination of 95% confidence interval (CI), calculation of odds ratio (OR) without taking into account the time of development of events of interest using 2x2 tables. The multivariate regression analysis included parameters that had clinical significance and statistical reliability. The coefficient of determination (R²) was taken into account from the parameters of the multivariate regression model. Differences or connections were considered statistically significant at $p < 0.05$.

The study was approved by the Ethics Committee of the St. Petersburg State Pediatric Medical University (Protocol No. 03/09 of 03/22/2021) for compliance with the provisions of the Helsinki Declaration on the Rights of the Patient.

Results and discussion: The analysis of the clinical manifestations of MIS-C revealed the most frequent clinical signs: fever (100%), conjunctivitis (84.8%), rash (78.9%), gastrointestinal symptoms (77.2%), cervical lymphadenopathy (66.9%), mucosal brightness (64%), hepatomegaly (64.4%), erythema/swelling

of the hands/feet (62.4%), sore throat (56.3%), facial swelling (50.5%), respiratory symptoms (49.4%), red cracked lips (49.3%), neurological symptoms (47.8%), hypotension/shock (43.8%), splenomegaly (40.7%), peeling fingers (35.7%), arthritis/arthritis (14.7%).

Among the laboratory parameters, most patients showed a significant increase in inflammatory markers, such as ESR, CRP, ferritin, hypoalbuminemia, hypoproteinemia, increased ALT, AST, LDH and D-dimer.

The following echocardiographic changes were noted: dilation/aneurysms of coronary arteries (16.2%), myocardial lesion (31.4%), pericardial effusion (29.5%). More than half of the patients (50.6%) were hospitalized in the intensive care unit. Glucocorticosteroids (81.5%), acetylsalicylic acid (57.1%), intravenous immunoglobulin (44.7%) were used to treat patients with MIS-C, and 4.9% of patients needed the anti-interleukin-6 biological therapy. The average length of hospital stay was 18 days.

Gastrointestinal disorders were represented by such features as abdominal pain (64.2%), vomiting (59.8%), diarrhea (69.6%) and peritoneal symptoms, which required diagnostic laparoscopy and removal of the appendix in 3 patients (1.8%). There was a predominance of boys in group 1 (64.8%) than in group 2 (40.5%),

Table 1

Comparative characteristics of patients with MIS-C, depending on the presence of symptoms of gastrointestinal tract damage

Parameters	The whole group (n=162)	1 group – with gastrointestinal involvement (n=125)	2 group - without gastrointestinal involvement (n=37)	p
Demographic indicators				
Age, months	98 (59; 134)	101 (60; 133)	96 (56; 141)	0.842
Gender, male, n (%)	96 (59.2)	81 (64.8)	15 (40.5)	0.008
Gender, female, n (%)	66 (40.8)	44 (35.2)	22 (59.5)	
Clinical and laboratory characteristics				
Neurological symptoms, %	47.5	51.6	33.3	0.053
Conjunctivitis, %	84.8	91.2	64.9	0.0001
Face swelling, %	50.5	56.5	30.8	0.022
Hepatomegaly, %	64.4	69.6	47.1	0.016
Splenomegaly, %	40.7	46	23.5	0.02
Hypotension/Shock, %	43.8	51.2	18.9	0.0005
C-reactive protein, mg/l	138 (44.0; 236.0)	157.7 (64.0; 238.0)	106.1 (31.0; 236.0)	0.077
Total protein, g/l	56.5 (49.0; 63.0)	55.6 (48.4; 62.8)	60.0 (53.0; 63.9)	0.081
Albumin, g/l	29.3 (25.8; 34.0)	28.8 (25.0; 33.2)	30.3 (28.3; 35.0)	0.034
Troponin, pg/ml	5.1 (1.0; 56.0)	7 (2; 90)	1 (0; 5)	0.065
ECHO-CG changes				
Coronary artery dilatation/CA aneurysms, %	16.2	15.3	19.4	0.551
Myocarditis, %	31.4	35	19.4	0.078
Pericarditis, %	29.5	30.8	25	0.501

Table 2

Factors associated with gastrointestinal tract damage in children with MIS-C

Parameter	Se	Sp	OR (95%CI)	p
Male gender	64.8	59.5	2.7 (1.3; 5.7)	0.008
Neurological symptoms	57.6	66.7	2.1 (0.98; 4.65)	0.053
Conjunctivitis	91.2	35.1	5.6 (2.2; 14.4)	0.0001
Face swelling	56.5	69.2	2.9 (1.1; 7.5)	0.022
Hepatomegaly	69.6	52.9	2.6 (1.2; 5.7)	0.016
Splenomegaly	45.9	76.5	2.8 (1.2; 6.6)	0.02
Shock/hypotension	51.2	81.1	4.5 (1.8; 11.0)	0.0005

Abbreviations: OR – odds ratio; CI – confidence interval; Se - sensitivity; Sp – specificity.

$p=0.008$). Hypotension or shock were significantly more common in patients of group 1 (51.2%) than in group 2 (18.9%, $p=0.0005$). There were differences in the frequency of neurological symptoms, which were more often observed in children of group 1 (51.6% vs. 33.3%, respectively, $p=0.053$). Among patients of the group 1 hepatomegaly (69.6% vs. 47.1%, $p=0.016$), splenomegaly (46% vs. 23.5%, $p=0.02$), conjunctivitis (91.2% vs. 64.9%, $p=0.0001$) and facial puffiness (56.5% vs. 30.8%, $p=0.022$) were observed more frequently.

Among laboratory abnormalities, patients of group 1 had a greater tendency to hypoalbuminemia (albumin - 28.8 g/l) than in group 2 (30.3 g/l, $p=0.034$), the level of CRP was significantly higher (157.7 mg/l vs. 106.1 mg/l, $p=0.077$), as well as troponin level (7 pg/ml vs. 1 pg/ml, $p=0.065$). Signs of myocardial damage were more common for group 1 patients (35% vs. 19.4%, $p=0.078$). The comparative characteristics between the two groups are presented in Table 1.

The next stage was the identification of clinical and laboratory signs associated with gastrointestinal tract damage using sensitivity analysis, specificity and calculation of odds ratio. The transformation of quantitative variables into qualitative ones was performed using AUC-ROC analysis. The results of the one-factor analysis are presented in Table 2.

Table 3

Factors associated with gastrointestinal tract damage in patients with MIS-C

Parameter	β	SE	p
Male gender	0.18	0.076	0.018
Conjunctivitis	0.27	0.075	0.0004
Shock/hypotension	0.27	0.075	0.0003

Characteristics with the highest sensitivity, specificity, odds ratio and clinical significance were included in the multivariate regression analysis. Of the initial 7 factors included in the model, only 3 variables were significantly associated with gastrointestinal tract damage: male gender, conjunctivitis and hypotension/shock. The results of multivariate regression analysis are presented in Table 3.

It is important to notice that gastrointestinal involvement in the pathological process is an extremely important early predictor of the possible severity of MIS-C, associated with such characteristics of the course of MIS-C as conjunctivitis, face swelling, central nervous system damage, hepatomegaly and splenomegaly, hypotension / shock, common for the severe course of the disease.

Discussion: The data obtained are comparable with studies previously published in the literature, however, it should be noted that there are not many publications of multicenter studies. Fever is described in 100% of cases in almost all studies. Most researchers note a high frequency of mucocutaneous manifestations (rash in 45-65% of cases, conjunctivitis in 30-81%, lip lesion in 27-76%) [7, 9, 6]. Many researchers note a fairly high frequency of hypotension or shock in patients with MIS-C (32-76%) [5, 6, 7, 9, 18]. Among laboratory changes, most researchers describe an increase in inflammatory biomarkers, thrombocytopenia, hypoalbuminemia, a significant elevation of D-dimer [17, 19, 6, 20]. The gastrointestinal disorders are noted in MIS-C in 71-86% of cases on average according to different researchers [9, 2], which is comparable with our data (77.2%). Among the examined patients with gastrointestinal involvement in our sample, three had acute appendicitis in the structure of the disease, which required laparoscopic appendectomy.

Similar cases are described in previously published works [10, 11, 16, 1].

Factors associated with gastrointestinal involvement (including a higher incidence of troponin levels and myocardial dysfunction) include an association with hypotension/shock and, apparently, gastrointestinal disorders can be caused by a decrease in mesenteric blood flow due to shock. However, there is also an opinion about the role of persistence of the SARS-Cov-2 virus in gastrointestinal tract, which can lead to local inflammation of the mucous membrane, increased release of zonulin and subsequent increased intestinal permeability for coronavirus antigens, including a superantigen-like motif of spike protein [21]. Face swelling in patients with MIS-C is also probably a consequence of hypoproteinemia, which is the result of shock / hypotension and, resulting from this, liver dysfunction. As for conjunctivitis, it refers to one of the signs of damage to the skin and mucous membranes due to systemic vasculopathy and is among the Kawasaki-like symptoms also characteristic of multisystem inflammatory syndrome.

Conclusion. In the conditions of still ongoing COVID-19 pandemic and, accordingly, the continuing risk of MIS-C morbidity, it is necessary to study the epidemiological history, conduct a thorough assessment of possible multiple lesions of organs and systems, paying special attention to abdominal symptoms. Gastrointestinal involvement is an extremely important early predictor of the severity of MIS-C, requiring subsequent careful clinical and laboratory monitoring and correction of therapy.

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