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Evaluation of the frequency, follow-up, and treatment of patients with multisystem inflammatory syndrome related to COVID-19

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Abstract

Aim: Aim of this study is evaluate the clinical features, laboratory values, treatment and follow-up of in children with COVID-19-associated multisystem inflammatory syndrome (MIS-C) disease.

Materials and Methods: In this study, patients aged between 2 months and 17 years, who applied to the Inonu University Faculty of Medicine, Department of Pediatrics between March 2020, and February 2021 due to MIS-C related to COVID-19 disease, were reviewed retrospectively. Demographic data, clinical features, laboratory values, treatment and follow-up data of the patients were evaluated.

Results: Forty-nine patients diagnosed with MIS-C between March 2020 and February 2021 were included in the study. Thirty-one (72.7%) patients were male and 18 (27.3%) were female. The most common indications for admission were fever (100%), abdominal pain (51.6%), vomiting (42.9%), cough (38.8%), diarrhea (28.8%), shortness of breath, rash, conjunctivitis, and convulsion. Levels of CRP (93.9%), D-dimer (85.7%), fibrinogen (73.4%), interleukin 6 (IL6) (73.4%), procalcitonin (71.4%), NT-proBNP (63.2%) remained at high levels in respective number of patients. The (32.6%) patients were followed up in the intensive care unit. These patients had cardiogenic shock (26.5%), severe pneumonia (18.3%), and acute gastroenteritis (14.3%). It was determined that the mean age of the patients followed up for cardiogenic shock was 12.5 years and relatively higher ($p<0.05$). One patient died during follow-up.

Conclusion: Although the manifestations of MIS- C due to COVID -19 are seen relatively rarely in children, it constitutes a serious problem and they mostly require hospitalization in intensive care unit, simultaneously involves many organ systems, and leads a serious course with higher risk of mortality. Another problem in these patients is higher rates of cardiac involvement. For this reason, it is important to take necessary precautions to protect children against COVID 19 and its associated MIS-C, and to include them in vaccination programs.

Introduction

COVID-19 is an infection that affected the whole world, and children since December 2019, causing a serious epidemic and millions of deaths. COVID-19 is caused by an enveloped, single-stranded RNA virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. This disease causes a serious and life-threatening disease characterized by acute respiratory distress syndrome (ARDS), septic shock, multi-organ failure, hypercoagulopathy and/or cytokine storm in approximately 10-20% of adults [3]. Compared to adults in the early stages of the pandemic, children were thought to have a milder illness and were less likely to be hospitalized [4-5].

However, later, a new clinical picture called multisystem inflammatory syndrome (MIS-C), which manifests with symptoms like Kawasaki disease in pediatric patients with coronary artery aneurysm, fever, mucocutaneous symptoms and hyperinflammatory symptoms, was defined [6-8].

Symptoms related to MIS-C mostly develop because of hyperstimulation of the immune system against viral infection. Hyperinflammation caused by the cytokine storm

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that occurs in adult COVID-19 patients with overactivation of the immune system is usually seen within 2 weeks, while MIS-C has been more commonly reported 2 weeks after the onset of SARS-CoV-2 infection [9-12].

In this study, we aimed to evaluate the demographic data, clinical features, laboratory values, treatment, and follow-up data of patients between the ages of 2 months and 17 years who met the clinical criteria of MIS-C and applied to our clinic due to COVID-19 disease between March 2020 and February 2021.

Materials and Methods

For this retrospective study, according to power analysis, the minimum sample size required to estimate the hospital admission rate of MIS-C patients with COVID-19 infection was calculated as 46 at the 95% confidence level, with a margin of 0.10 deviation. Total population sampling was used and all the 49 patients who met our inclusion criteria were included in the study.

In this study, patients between the ages of 2 months and 17 years, who applied to the Inonu University, Faculty of Medicine, Department of Pediatrics between March 2020, and February 2021 due to COVID-19 disease, were retrospectively analyzed. Diagnosis of MIS-C was made according to the criteria defined by WHO (Table 1). Demographic data, clinical findings, laboratory values, echocardiography, electrocardiography results, length of hospital stay, requirements for intensive care hospitalization, treatments and follow-up findings of the patients.

The treatment of the disease was arranged by considering the treatment guide of the Ministry of Health and current literature. Intravenous inotropic therapy was initiated in accordance with the clinical status of the patients with hypotensive course and concomitant heart failure findings and circulatory disorders. Intravenous immunoglobulin (IVIG) treatment was routinely started in all patients diagnosed with MIS-C. Patients who had lung infections but whose general condition was stable or who tolerated oxygen therapy with a mask were followed up in the service. The criteria for admission to the intensive care unit were determined according to the presence of hypoxemia, hypotension requiring inotropic support, and circulatory disorder, the severity of organ involvement, and the clinical findings of the patients. Patients with MIS-C syndrome findings but staphylococcal growth in their blood cultures were defined as cases with toxic shock syndrome. Patients presenting with toxic shock syndrome and macrophage activation syndrome (MAS) groups were excluded from the study.

Statistical evaluation

IBM SPSS Statistics for Windows version 22.0 (NY, USA) was used for statistical analysis. Normality of the quantitative data was evaluated by Shapiro-Wilk test. Continuous data were summarized with median, minimum, and maximum values, categorical data were presented as counts and percentages. Since the normality assumption was violated, comparison of two independent groups according to quantitative data was made using Mann-Whitney U test. Comparisons of categorical variables were made using Pearson's chi-square test, continuity-corrected chi-square test or Fisher's exact test where appropriate. In all analyzes $p<0.05$ were considered significant. The treatments of the patients were planned in accordance with the guidelines of the Ministry of Health and in consideration of the clinical status of the patients.

Our study was carried out in accordance with the principles stated in the latest version of Declaration of Helsinki, published in 2013, after obtaining the consent of the patients and the approval of the ethics committee. Approval was obtained from the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 23.03.2021, Decision no 2021/1770).

Results

The total of 56 patients who applied with the diagnosis of COVID-19 but received the diagnosis of MIS-C between February 2020 and March 2021 were analyzed. However, among these patients, a patient with a brain tumor who had COVID-19 and received chemotherapy with the presumptive diagnosis of hyperinflammatory syndrome, the patients followed up for diabetic ketoacidosis (n=1), for acute lymphoblastic leukemia (ALL) (n=1), a patient receiving chemotherapy, and a patient diagnosed with macrophage activation syndrome were excluded the study.

After exclusion of these patients, the remaining 49 patients including 31 (72.7%) male, and 18 (27.3%) female cases were enrolled in the study. The median age of the patients was 7.3 years (3 months-17 years). The median weight of the patients was 28 (4-75) kg, and the median body mass

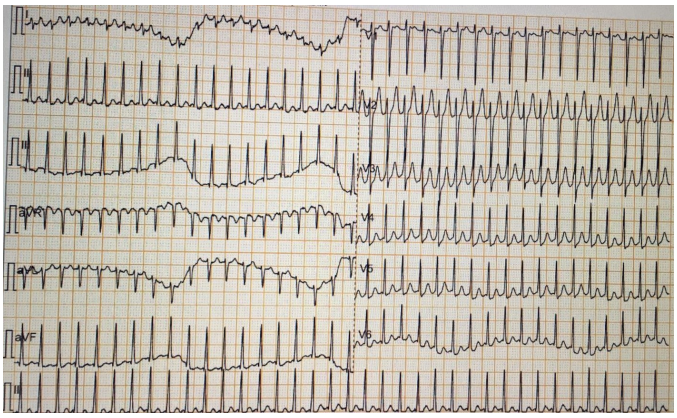

Figure 1. ECG of a patient with supraventricular tachycardia.

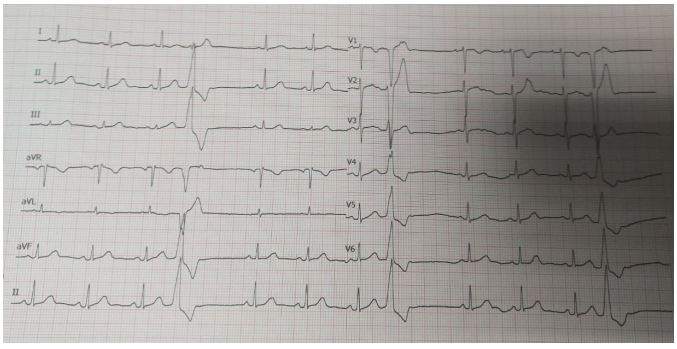

Figure 2. ECG of a patient with ventricular ectopy.

Table 1. Diagnostic criteria of MIS-C established by World Health Organization (WHO) and USA Disease Control, and Prevention Centers (CDC).

	WHO	CDC
Age (years)	0-19	<21
Clinical manifestations		
	Fever > 3 days 2 of the following criteria:	
	Rashes or signs of bilateral non-purulent conjunctivitis or mucocutaneous inflammation Hypotension or shock; Myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities or Increased levels of troponin or N-terminal pro B type natriuretic peptide Evidence of coagulopathy; Increased prothrombin time, partial thromboplastin time and D-dimer values and	History of subjective or objective fever ($\geq$ 38,0oC) lasting for at least 24 hours and Manifestations of severe disease state requiring hospitalization and Involvement of $\geq$ 2 organs Cardiovascular system; Shock, increased troponin, BNP levels, abnormal echocardiography findings, arrhythmia, Respiratory system; Pneumonia, acute respiratory distress syndrome, pulmonary embolism Renal; Renal failure Hematologic findings; coagulopathy, increased D-dimer levels Gastrointestinal findings; (increased liver enzymes, diarrhea, ileus, Dermatologic findings; erythroderma, mucositis, rashes, Neurologic findings; (convulsion, stroke, aseptic meningitis
	Acute gastrointestinal problems;	One or more than one criteria as follows:
	Diarrhea, vomiting or abdominal pain and Increased levels of acute phase reactants as ESR, CRP, procalcitonin	Increased CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH or IL-6; neutrophil counts or lymphopenia, hypoalbuminemia
PCR		
	Positive RT-PCR, antigen test or serology or contact with COVID-19 disease patient(s)	Positive RT-PCR, antigen test or serology or contact with COVID-19 disease patient(s) 4 weeks before onset of symptoms
	Lack of any alternative diagnosis	Lack of any alternative diagnosis

Table 2. Demographic data of the patients with MIS-C.

Demographic characteristics, and accompanying diseases	average /ratio
Age 7.3 years	(0,3-17 years)
Gender (male/female)	31/18
Body weight (kg)	28 (4-75)
Body mass index (kg/m^2)	17.4 (12.6-31.7
Accompanying disease, n (%)	9 (18.4)
Overweight	2 (4.1)
Obesity	2 (4.1)
Asthma bronchiale	1 (2.0)
Esophageal atresia	1 (2.0)
Immune deficiency	1 (2.0)
Congenital heart disease	1 (2.0)

index was 17.4kg/m^2 (12.6-31.7 kg/m2). Nine (18.4%) patients had other accompanying diseases. Demographic data of the patients and accompanying diseases are shown in Table 2.

The most common symptoms were fever (100%), abdominal pain (51.6%), vomiting (42.9%), cough (38.8%), diarrhea (28.8%), shortness of breath, rash, conjunctivitis, and convulsion. It was found that the complaints of fever in the patients generally started 2-7 days before admission to the hospital. In the physical examination of the patients, abdominal tenderness was found in 55.1%, rales in 38.7%, skin and mucosal rashes in 26.5% and a murmur in 14.2% of the cases (Table 3). At the time of admission to the hospital; significant lymphopenia was detected in 22 (% 44.9), and increased levels of liver enzymes was detected in 15 of them (%30.6). CRP was increased in 46 (93.9%), D-dimer in 42 (85.7%), fibrinogen and interleukin 6 (IL-6) in 36 (73.4%) and procalcitonin in 35 (71.4%) patients. In addition, increased the levels of ferritin and INR were detected in 23 (46.9%), NT-proBNP in 31 (63.2%), and troponin I in 8 (16.3%) patients. SARS-CoV-2 PCR positivity was detected in 19 (38.8%), and SARS-CoV-2 Serology positivity in 26 (53.1%) patients.

On ECG, arrhythmia was detected in two, supraventricular (SVT) tachycardia, and moderate ventricular ectopy in one patient. Laboratory findings of the patients are given in Table 4.

Lung infection was detected in the chest X-rays of 13 (26.5%) of 19 (38.7%) patients, and an appearance compatible with COVID-19 pneumonia was detected in nine (18.4%) patients on thorax computed tomography. Signs of ARDS were revealed in four (14.3%) patients. In addition, significant pleural effusion was detected in six

Table 3. Admission complaints, and clinical characteristics of the patients.

Symptoms, and clinical findings of the patients	Number of patients (49)	%
Fever	49	100
Abdominal pain	27	55.1
Vomiting	21	42.9
Cough	19	38.7
Diarrhea	14	28.8
Dyspnea	9	18.4
Rashes	9	18.4
Conjunctivitis	6	12.2
Strawberry tongue	4	8.2
Seizure	4	8.2
Abdominal tenderness	27	55.1
Rales	19	38.7
Cutaneous and mucosal rashes	13	26.5
Murmur	7	14.3

Table 4. Laboratory values of the patients.

Parameters	Reference range	Average value	Maximum-minimum values
Leucocyte	4.3-10.3	11.80	1.43 – 32.91
Hemoglobin (gr/dL)	13.6-17.2	12.1	7.9 – 15.2
Hematocrit (%)	39.5-50.3	34.5	22.6 – 47.8
Platelet (10^3)	156-373	286	78 – 1595
Lymphocyte (10^3)	1.3-3.5	1.58	0.22 – 9.50
AST (U/L)	5-34	40	14 – 1887
ALT (U/L)	0-55	36	8 – 2556
LDH (U/L)	29-155	305	15 – 1535
Amylase(U/L)	25-125	55	7 – 607
Lipase (U/L)	8-78	31	5 – 2348
C-Reactive protein (mg/dL)	0-0.351	7.78	0.30 – 282.00
Procalcitonin (ng/mL)	0-0.5	2.84	0.02 – 100.00
Fibrinogen (mg/dL)	150-150	492	119 – 1344
IL-6 (pg/mL)	0-7	62.8	1.5 – 2671.0
Ferritin (ng/mL)	10-291	295	5 – 1650
INR	0.8-1.2	1.13	0.82 – 5.55
D-dimer (mg/L) FE	0-0.55	3.64	0.19 – 37.90
Troponin I (pg/mL)	0-15.6	2.75	0.40 – 1146.00
NT-proBNP (pg/mL)	0-125	316	20 – 35000

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; IL, interleukin; INR, international normalized ratio.

(12.3%) patients.

On echocardiographic evaluation of the patients, coronary artery dilatation with a z score >2.5 was detected in seven (14.3%) patients. Severe myocarditis was detected in four, pericardial effusion in three, and mitral regurgitation (MR) due to mitral valve involvement in one patient. The clinical course of the patients and the treatments are given indicated in Table 5.

Sixteen of the patients with poor general condition, marked hypotension, circulatory disorder requiring high flow oxygen therapy or mechanical ventilation, were followed up in the intensive care unit. Among the patients admitted to the intensive care unit, 13 were male and three were female. Nine of these patients were followed up for severe pneumonia and four of them for ARDS. Six patients had concomitant severe acute gastroenteritis, seven patients had severe hypotension and circulatory disorder requiring inotropic therapy. In addition, encephalitis was detected in one patient and this patient was followed up in the intensive care unit. Eight of the patients treated in the intensive care unit received high flow oxygen therapy, and four patients were intubated and followed up connected to a mechanical ventilator Cardiogenic shock was present in 13 of 16 patients with hypotension. Seven (53.2%) of the patients with cardiogenic shock were followed up in the intensive care unit. Drugs such as dopamine, dobutamine, adrenaline, noradrenaline and milrinone were started as IV inotropic support for the patients presenting with monitored cardiogenic shock according to the clinical condition of the patient. In addition, tocilizumab was given for five patients and pulse steroid therapy for nine patients. Three of these patients received high flow oxygen therapy and three of them were intubated and monitored with mechanical ventilator. Furosemide and spironolactone treatments were started in addition to their current treatment in patients with pericardial effusion. Among the patients included in the study, the mean age of the patients followed up for cardiogenic shock was found to be higher (mean 12.5 years and $p<0.05$). In addition, laboratory values of

Table 5. Clinical course of the patients.

Disease /hospitalization/treatment	Patients (n)	%
Pneumonia	19	38.7
AGE	14	28.8
ARDS	4	8.2
Pleural effusion	6	12.2
Pancreatitis	3	6.1
Kawasaki disease	7	14.3
Coronary involvement	7	14.3
Myocarditis	4	8.2
Pericardial effusion	3	6.1
Valvular involvement	1	2.0
Arrhythmia	2	4.1
Convulsion	3	6.1
Need for intensive care unit	16	32.7
High-flow oxygen therapy	8	16.3
Intubation	4	8.2
IVIG	49	100
Pulse steroid	9	18.4
Steroid	32	65.3
Tocilizumab	5	10.2
Antibiotics	47	95.9
Low-molecular weight heparin	9	18.4
Aspirin	9	18.4
Duration of hospitalization (days)	9 (3 -53)	
Exitus	1	2.0

AGE, acute gastroenteritis; ARDS, acute respiratory disease syndrome; IVIG, intravenous immunoglobulin.

Table 6. Comparison of patients with and without cardiogenic shock.

	Group with cardiogenic shock (n=13)	Group without cardiogenic shock (n=36)	p
Gender (Male/Female)	9/4	22/14	0.743
Age (years)	12.5 years (2 mos – 17 yrs)	4.3 years (2mos – 17 yrs)	0.007*
Overweight	2 (15.4%)	0 (0%)	0.602
Obesity	0 (0%)	2 (5.6%)	0.602
Leucocyte	11.10 (1.43 – 24.68)	12.32 (3.20 – 32.91)	0.746
Hemoglobin	11.9 (7.9 – 13.7)	12.3 (8.7 – 15.2)	0.527
Platelet	254 (78 – 1595)	287 (98 – 719)	0.332
Lymphocyte	1.52 (0.22 – 5.56)	1.70 (0.38 – 9.50)	0.557
Lymphopenia	5 (38.5%)	17 (47.2%)	0.748
CRP	11.70 (0.40 – 282.00)	7.33 (0.30 – 34.70)	0.385
Procalcitonin	10.80 (0.09 – 55.59)	2.12 (0.02 – 100.00)	0.362
IL-6	51.5 (6.2 – 1396.0)	74.2 (1.5 – 2671.0)	0.687
Fibrinogen	617 (119 – 1344)	486 (125 – 765)	0.227
Ferritin	522 (59 – 1650)	210 (4 – 1650)	0.011*
Ferritin >500	9 (69.2%)	7 (19.4%)	0.004*
INR	1.34 (1.10 – 5.55)	1.10 (0.82 – 2.47)	0.001*
D-dimer	5.60 (0.91 – 37.90)	3.34 (0.19 – 20.80)	0.207
ALT	91 (21 – 613)	25 (8 – 2556)	0.003*
Lipase	63 (21 – 2348)	28 (5 – 211)	0.016*
ProBNP	488 (38 – 35000)	313 (20 – 8953)	0.197
Troponin	87.10 (1.40 – 800.00)	2.50 (0.40 – 1146.00)	0.019*
ECHO			
Normal	5	29	0.002*
Myocarditis	4	0	
Pericardial effusion	2	1	
Coronary involvement	2	5	
Valvular involvement	0	1	
ICU stay	7 (53.8%)	9 (25.0%)	0.143
High-flow O_2 therapy	3 (23.1%)	5 (13.9%)	0.663
Intubation	3 (23.1%)	1 (2.8%)	0.052
Duration of hospitalization	10 (3 – 20)	7 (3 – 53)	0.087

CRP, C-reactive protein; INR, International Normalized Ratio, ALT, alanine aminotransferase; ECHO, echocardiography; ICU, intensive care unit; ProBNP, N-terminal pro B type natriuretic peptide.

ferritin, INR, ALT, lipase, and troponin I were found to be significantly higher than in other patients ($p<0.05$). The data of patients with and without cardiogenic shock are compared in Table 6.

Intravenous immune globulin was started in all of the patients we followed up with the diagnosis of MIS-C, and antibiotic treatment was started in 47 patients. A maintenance dose (2 mg/kg) of steroid treatment was started in 32 patients who were followed up, and pulse steroid treatment was given to nine patients (30 mg/kg) according to their clinical status. In addition, depending on the clinical course and condition of the patients, tocilizumab treatment was given to five patients, and low molecular weight heparin and aspirin therapy to nine patients. Anti-inflammatory aspirin therapy was started in patients with a clinical picture like Kawasaki syndrome.

Discussion

In the studies conducted and, in the reports, presented so far, the incidence of the disease is estimated to be 2 per 100,000 people under the age of 21, and the overall incidence in children with COVID-19 is 322 per 100,000 people (13-16). Although the average age of MIS-C patients varies between 2-16 years, it can also be seen at younger ages (6-8). The most prominent finding in these patients is fever. Fever is detected in almost all the patients. In addition, gastrointestinal findings such as vomiting, diarrhea, abdominal pain, rash, conjunctivitis, hand-foot edema, mucocutaneous symptoms such as red-chapped lips and strawberry tongue, neurological findings such as headache, irritability, personality changes, and encephalopathy can be observed [12,17].

The most common symptoms detected in our patients were fever (100%), abdominal pain (51.6%), vomiting (42.9%), cough (38.8%), diarrhea (28.8%), shortness of breath, rash (%) 18.4), conjunctivitis (12.2%) and convulsion. Hypotension was found in 32.6%, cardiac involvement in 30.6%, lung involvement in 38.8%, and acute gastroenteritis (AGE) in 28.8% of the patients. In laboratory tests, the most common findings were CRP elevation in 93.9%, higher levels of D-dimer in 85.7%, fibrinogen and interleukin 6 (IL-6) in 73.4%, procalcitonin in 71.4% of the

patients. In addition, increased levels of ferritin and INR were observed in 46.9%, NT-proBNP in 63.2% and troponin I in 16.3% of the cases. SARS-CoV-2 PCR positivity was detected in 38.8% and SARS-CoV-2 serology positivity in 53% of the patients.

Patients followed up for MIS-C have symptoms similar to Kawasaki disease, accompanied by significant fever, diarrhea, vomiting, skin and mucosal rashes, and coronary artery aneurysm. In addition, the presence of severe lung infection findings such as pneumonia and ARDS, and the presence of disease symptoms such as hypotension, myocarditis, pericardial and pleural effusion carry importance in terms of showing the challenging difficulties encountered during treatment and follow-up of this newly defined disease with multi-organ involvement.

Although the causes of MIS-C disease that occurs after COVID-19 infection are not clear, there are findings suggesting cytokine storm as its etiologic factor. The presence of increased cytokine levels together with the presence of COVID-19 infection, especially high levels of interleukin 6 (IL6) in these patients, and the presence of various antibodies associated with this condition, suggested that the immune cell-mediated cytokine storm of MIS-C is an antibody-mediated process [18].

Although COVID-19 infection shows respiratory system tropism [19] in MIS-C disease, in which cardiovascular, gastrointestinal, skin rash and neurological problems are more prominent, respiratory symptoms, were found to be at a lower rate compared to COVID-19 disease [20,21]. Hypotension was found in 32.6%, cardiac involvement in 30.6%, lung involvement in 38.8%, AGE in 28.8%, skin and mucosal rash in 26.5% of our patients. In studies, gastrointestinal symptoms were detected in approximately 70% of patients. Usually, gastrointestinal symptoms such as vomiting, diarrhea, abdominal pain and mesenteric lymphadenopathy are seen [6,22,23].

When patients with MIS-C were evaluated, cardiovascular abnormalities were detected in approximately 70% of the patients. The most common findings were tachycardia, left ventricular dysfunction, myocarditis, cardiovascular abnormalities such as coronary artery dilatation or aneurysm, hypotension, pericardial effusion or valve insufficiency (15,20,23-25). Most patients had symptoms similar to Kawasaki disease such as polymorphic skin rash, changes in mucous membranes (chapped lips, strawberry tongue), non-purulent conjunctivitis, and lymphadenopathy. These symptoms were detected in approximately 43-70% of patient (18,20,26). Respiratory symptoms were detected in 33-60% of the patients; these were upper respiratory tract symptoms, dyspnea, and pulmonary infiltrative findings [20,22].

Gastrointestinal symptoms were the 2nd most common symptoms including abdominal pain in 55.1%, vomiting in 42.9%, diarrhea in 28.8%. The most common respiratory disorders were pneumonia in 38.8%, shortness of breath in 18.8%, and pleural effusion in 12.2% of the patients. Skin and mucosal rashes were detected in 26.5%, and conjunctivitis in 12.2 % of our patients. In 30.6% of our patients' symptoms and signs related to the cardiovascular system were detected. The most common symptoms and signs of cardiovascular system were coronary artery aneurysm, myocarditis, pericardial effusion, and valve involvement. In addition, 32% of the patients had hypotension and 26.5% of them had cardiogenic shock findings.

Although the white blood cell counts were increased, lymphocytopenia was commonly detected, and anemia and thrombocytopenia were also shown among other hematological parameters. Biomarkers showing inflammation were found to be high in all patients. C-reactive protein (CRP), IL6, and ferritin, and procalcitonin levels were higher in these patients, in addition to inflammatory markers, markers involving in coagulation such as D-dimer and fibrinogen, and cardiac biomarkers such as troponin and proBNP, which indicate myocardial damage were also increased in these patients [18,23,25,27,28]. Increased levels of CRP were detected in 93.9%, D-dimer in 85.7%, fibrinogen, and IL6 in 73.4%, procalcitonin in 71.4%, and ferritin in 46.9% of our patients. NT-proBNP showing myocardial damage was detected in 63.2% and troponin I in 16.6% of the patients. Lymphopenia was detected in 46.6%, increased INR in 32.6, and elevated liver enzymes in 30.2% of the patients. The detected laboratory findings were similar when compared with the literature.

There is no standard treatment for MIS-C, but some treatments have been suggested due to COVID-19 positive seroconversion and high detection of inflammatory markers, and the event is thought to be part of the inflammatory process. In this respect, most frequently IVIG and corticosteroids have been used for treatment [24,29,30]. In addition, IL6 receptor antibody, IL1 receptor antagonist, monoclonal antibodies against tumor necrosis factor have been used and tested in the treatment [30]. There is no consensus on these treatments. Treatments can be applied according to the availability of the drug, the status of cytokines and inflammatory markers, and the clinician's preference. Intravenous immunoglobulin treatment was started in all of the patients we followed.

In addition, steroid treatment was given to 65.3% of the patients, but pulse steroid treatment was started in 9 (18.3%) patients whose conditions were severe and whose complaints of fever could not be controlled.

In addition, 5 (10.2%) of our patients with severe pneumonia were given tocilizumab treatment. Low molecular weight heparin treatment was started in 9 (18.4%) patients who showed signs of hypercoagulation. In addition, 9 (18.4%) patients with clinical symptoms similar to Kawasaki syndrome were given aspirin therapy.

The average length of hospital stay was 7.5 days for patients hospitalized in the ward, and 11.5 days for patients hospitalized in the intensive care unit. Cardiac functions were followed up continuously with echocardiography during the hospitalization period. The patients were discharged after their cardiac pathologies improved and the levels of cardiac biomarkers as troponin I and NT-proBNP returned to normal. Patients with myocarditis, pericardial effusion and valve involvement and patients with coronary artery dilatation were followed up for 15 days, 1, 3, 6 months and 1 year after their discharge. Multisystem inflammatory syndrome is thought to believe to occur secondary to the post-infection inflammatory response following COVID-19 infection, seems to be clinically and laboratory different when compared to COVID-19 infection.

Although MIS-C is less frequently seen, the higher need for intensive care, involvement of multiple systems, the severe course of the disease and the higher risk of death are causes of serious concern. In addition, increased cardiac involvement in these patients is a striking feature.

Multisystem inflammatory syndrome had undeniable similarities with hyperinflammatory syndromes such as Kawasaki disease, Hemophagocytic lymphohistiocytosis (HLH), MAS, and toxic shock. As with other syndromes, high levels of many markers of nonspecific inflammation do not create sensitivity or specificity for this syndrome. Therefore, the treatment methods used for other hyperinflammatory syndromes were modified and applied in MIS-C. Considering the low number of patients, the fact that more severe cases apply to our hospital because our hospital is a tertiary hospital, and patients with mild disease may have received treatment in other hospitals, this situation constitutes the limitations of our study.

Conclusion

Although the MIS-C manifestations seen in children due to COVID -19 is relatively rare, it is a serious problem due to increased need for intensive care, involvement of many systems, quite serious course of the disease and higher risk of death. Another problem in these patients is higher cardiac involvement. In our study, it was determined that fever was present in all patients, as well as gastrointestinal symptoms were found at a high rate and MIS-C has critical importance in terms of cardiac involvement and need for hospitalization in the intensive care unit. We have determined that these patients need serious intensive care support, required to close follow-up, and treatment. We also believe that long-term follow-up is required to determine and treat long-term sequelae of the disease and outcomes of cardiac pathologies.

Larger -scale multicenter studies are still needed to determine the treatment strategies of MIS-C all over the world. Considering the severity of the disease, it is important to take the necessary precautions to protect children against COVID-19 and its associated MIS-C, and to include them in vaccination programs.

Ethics approval

Ethical approval for this study was obtained from the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 23.03.2021, Decision number 2021/1770).

Disclosure

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