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ORIGINAL ARTICLE

Readmission reasons of pediatric patients diagnosed with multisystem inflammatory syndrome after discharge

Ela Cem[1], Elif Kıymet[1], Elif Böncüoğlu[1], Şahika Şahinkaya[1], Miray Yılmaz Çelebi[1], Mustafa Gülderen[1], Aybüke Akaslan Kara[1], Timur Meşe[2], Hasan Ağin[3], Nuri Bayram[1], İlker Devrim[1]

[1]*Department of Paediatric Infectious Diseases, University of Health Sciences, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Izmir, Türkiye*

[2]*Department of Paediatric Cardiology Diseases, University of Health Sciences, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Izmir, Türkiye*

[3]*Department of Paediatric Intensive Care, University of Health Sciences, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital, Izmir, Türkiye*

ABSTRACT

Objectives: There is no clear information in the literature about causes of reactivation of multisystem inflammatory syndrome in children (MIS-C) or indications for readmissions for MIS-C after discharge; as a result, the conditions that may develop after infection in children with MIS-C were discussed, and the reasons for hospitalization were screened.

Patients and methods: This single-center retrospective study was conducted with 95 patients (65 males, 30 females; mean age: 92.8±55.5 months; range, 5 to 17 months) between November 11, 2020, and December 30, 2021. Children who were rehospitalized in the study center after their discharge with the diagnosis of MIS-C were included in the study, and the indications for readmissions were evaluated.

Results: During the study period, six (6.3%) patients (4 males, 2 females; median age: 114.5 months [interquartile range: 122 months]) had to be rehospitalized. Four of these patients had an underlying disease, while the other two were previously healthy children. Fever was the most common reason for readmissions in half of the patients, while the remaining patients were readmitted with the indications of myocarditis, pneumonia, and posttraumatic pain syndrome.

Conclusion: Although no evidence for the reactivation of MIS-C was detected in patients in the literature, it should also be emphasized that close follow-up of these patients is a must, considering possible cardiac complications.

Keywords: Children, MIS-C, multisystem inflammatory syndrome, rehospitalization.

Due to severe cardiac involvement, such as myocarditis, multisystem inflammatory syndrome in children (MIS-C) has emerged as an important complication associated with coronavirus disease 2019 (COVID-19). Although it is thought that pediatric patients are not vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as adults in the early stages of the pandemic, MIS-C is a severe and uncontrolled inflammatory response with multiorgan involvement that occurs weeks after the onset of SARS-CoV-2 infection.[1]

The long-term effects of this inflammatory response on organs are not yet known. In the

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Correspondence: Ela Cem, MD. SBÜ, Dr. Behçet Uz Çocuk Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi Çocuk Enfeksiyon Hastalıkları Kliniği, 35210 Konak, İzmir, Türkiye. E-mail: elabezirkn@hotmail.com

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foreground, there are publications on the clinical findings, immunopathogenesis, and management of the disease.[2,3] Recent studies on this disease and its potential long-term complications have been published in peer-reviewed journals.[4,5] As a result, patients should be monitored for long-term complications after discharge. To the best of our knowledge, there have been adult studies on COVID-19-related rehospitalizations, but no specific information on clinical characteristics of patients and hospital readmission rates after discharges of children with MIS-C is available.[4] Thus, the aim of this study was to evaluate and describe the rates and indications for rehospitalizations and long-term complications in patients who had been previously hospitalized with MIS-C.

PATIENTS AND METHODS

This single-center retrospective study was conducted with 95 patients (65 males, 30 females; mean age: 92.8±55.5 months; range, 5 to 17 months) diagnosed with MIS-C and admitted to a tertiary children's hospital in Izmir, Türkiye, between November 11, 2020, and December 30, 2021. The patients who were diagnosed with MIS-C were followed up for at least one month following discharge in terms of the indications for hospitalization. Although 104 patients were initially enrolled in the study, nine patients were excluded as they could not be followed up (Table 1).

In the study, all patients hospitalized in the pandemic clinic fulfilled the case description

Table 1. Demographics and admission characteristics of children hospitalized with MIS-C

	n	%	Mean±SD
Number of patients hospitalized diagnosed with MIS-C	104		
Number of patients excluded from the study	9		
Number of patients included in the study	95		
Sex			
Male	65	68.4	
Female	30	31.4	
Age (month)			92.8±55.5
Duration of fever before the diagnosis (day)			12.0±5.1
Duration of fever during hospitalization (day)			5.0±1.1
Duration of hospitalization			9.56±3.77
SARS-CoV-2 serology positivity	90	94.7	
Patients with underlying disease	5	5.2	
Number of patients who had IVIG administration	95	96.9	
Number of patients who had steroid administration	54	55.1	
Presenting signs and symptoms			
Shortness of breath	7	7.4	
Cardiac involvement (hypotension, tachycardia)	21	22.1	
Gastrointestinal involvement	34	35.8	
Cutaneous manifestations	31	32.6	
Conjunctivitis	30	31.6	
Headache	6	6.3	

MIS-C: Multisystem inflammatory syndrome in children; SD: Standard deviation; IVIG: Intravenous immunoglobulin.

of MIS-C according to the Centers for Disease Control and Prevention and World Health Organization criteria.[4,6,7] Accordingly, diagnosis of MIS-C was made for individuals aged <18 years presenting with fever >38.0°C for ≥24 h, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological). In addition, these patients had no plausible alternative diagnoses, and each patient had current or recent SARS-CoV-2 infection based on real-time polymerase chain reaction, serologic tests, or exposure to a suspected or confirmed COVID-19 case within four weeks prior to the onset of symptoms. Cases that did not meet the above criteria were excluded from the study.

All patients with the diagnosis of MIS-C were followed up after discharge. Initially, visits were scheduled after discharge at least within 15 days. They were also followed up once a month for a year. During that time, we investigated the indications for rehospitalizations and the outcomes.

Data on demographic and clinical parameters (age, sex, symptoms, and medical history), underlying diseases, and evidence of SARS-CoV-2 polymerase chain reaction positivity or past SARS-CoV-2 exposure, as well as the length of the first and second hospitalization, were collected from patients' medical records with their consent. Following discharge, patients' examination, hemogram, blood levels of urea, creatinine, aspartate transaminase, alanine aminotransferase, albumin, treatment process, and follow-up were recorded. Finally, the indications for hospital readmissions after MIS-C diagnosis and whether there was evidence for the reactivation of MIS-C were scanned and recorded.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Numerical data with normal distribution were expressed as mean ± standard deviation (SD), while numerical data with nonnormal distribution were expressed as median (interquartile range; IQR). A chi-square test was used to investigate the correlations among variables. The level of statistical significance was set at $p<0.05$.

RESULTS

Of the 95 patients, SARS-CoV-2 serology was positive in 94.7%. While 90 patients diagnosed with MIS-C were previously healthy, the remaining five patients had underlying diseases, including osteopetrosis, prematurity, cerebral palsy, vesicoureteral reflux, and asthma. Considering the complaints and clinical features of these patients, the mean of febrile days before diagnosis was 12.0±5.1 days, and the mean of febrile days during hospitalization was 5.0±1.1 days. Respiratory distress was present in seven (7.4%), hypotension and tachycardia in 21 (22.1%), gastrointestinal involvement in 34 (35.8%), cutaneous manifestations in 31 (32.6%), conjunctivitis in 30 (31.6%), and headache in six (6.3%) patients. While 49 (51.6%) patients had cardiac involvement with systolic dysfunction, the remaining 46 (48.4%) patients had no cardiac involvement. Ninety-five (96.9%) patients had received intravenous immunoglobulin, and 54 (55.1%) received steroid therapies. All patients survived up to hospital discharge. Table 1 summarizes the demographics and admission characteristics for children hospitalized with MIS-C.

Patients were followed up for a median period of four months (range, 15 days to 7 months). Cardiac findings (the most common of which was valve involvement) persisted in 20 patients on their first visit, but they were detected in only four patients on their last visit. Two of the four patients had mitral regurgitation, and their follow-up was continued, while the remaining two patients were hospitalized. During the study period, six (6.3%) patients with MIS-C were rehospitalized after discharge. Four of these patients were male (66.6%), and two were female (33.3%). Their median age was 114.5 months (IQR: 122 months). Two patients had an underlying diagnosis of cerebral palsy and osteopetrosis. These two patients were rehospitalized for pneumonia; thus, they are not detailed in the text as their rehospitalizations were unrelated to MIS-C. The reasons for rehospitalizations of the remaining four patients were considered to be related to MIS-C.

Table 2. Clinical characteristics and rehospitalization reasons of patients associated with MIS-C

Patients characteristics			First admission				Second admission			
Case number	Sex	Age (year)	Length of first hospital stay (days)	Underlying diseases	COVID-19 serology positivity	Admission to the intensive care unit	Time from discharge to second hospitalization (days)	Reason of second admission to hospital	SARS-CoV-2 PCR positivity
Case 1	F	2	7	VUR	COVID-19 IgG (+), IgM (-)	None	12	Febrile convulsion, diarrhea	None
Case 2	M	11 months	20	Prematurity	COVID-19 IgG (+), IgM (-)	None	3	Elevated cardiac enzymes	None
Case 3	M	8	8	None	COVID-19 IgG (+), IgM (-)	None	21	Fever, pre-planned cardiac imaging	None
Case 4	M	14	16	None	COVID-19 IgG (+), IgM (-)	Yes	6	Post-traumatic pain syndrome	None

MIS-C: Multisystem inflammatory syndrome in children; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PCR: Polymerase chain reaction; VUR: Vesicoureteral reflux; IgG: Immunoglobulin G, IgM: Immunoglobulin M.

Among these four patients, the first case was of a two-year-old female patient who had underlying vesicoureteral reflux disease. The patient presented with febrile convulsions and accompanying diarrhea on the 12th day of discharge. Fever and diarrhea did not persist during the patient's hospitalization. The second patient, with the underlying disease of prematurity, was monitored due to a six-fold increase in cardiac enzymes in the follow-up period after discharge; consequently, treatment with a beta-blocker was started. This patient's cardiac enzymes returned to normal within three weeks of hospitalization, and concurrent cardiac echocardiography was normal. The third previously healthy patient was rehospitalized due to a febrile episode. Owing to the irregular use of aspirin medication and the detection of coronary involvement in echocardiography at the time of admission, a preplanned cardiac magnetic resonance imaging (MRI) was performed. The patient's cardiac MRI did not demonstrate any signs of scarring or fibrosis, and troponin values were within normal limits at admission and during the follow-up. The fever of the patient, who was followed up with only supportive treatment, did not persist. The last patient, who was also previously healthy, was admitted to the intensive care unit due to MIS-C and readmitted due to weakness and soreness in the lower extremities. In terms of demyelinating neurological diseases, electroencephalography and electromyography were unremarkable. The patient's symptoms of weakness resolved after 24 h with complete clinical improvement. The patient was diagnosed with posttraumatic pain syndrome as a result of a history of intensive care unit admission with the diagnosis of MIS-C. Table 2 summarizes the distribution of the reasons for the second hospitalization after discharge with the diagnosis of MIS-C.

DISCUSSION

A few treatment algorithms have been described in the literature since the description of MIS-C in mid-April 2020; however, an algorithm for postdischarge follow-up has not yet been determined, and data on relatively longer-term outcomes of MIS-C are limited.[8] The current study has discussed the postdischarge follow-up

processes of all patients hospitalized with the diagnosis of MIS-C. Only six of the 95 patients who were followed up after discharge required rehospitalization, and no pathology was found in the laboratory and physical examination findings of the remaining patients. Consistent with the other reports in the literature, the cardiac involvement of the patients continued after discharge; however, the echocardiographic findings in three of the four cases completely regressed in the follow-up.[9]

In the current study, four patients were rehospitalized after discharge. Unlike our report, Farooqi et al.[10] observed that no child was readmitted to the hospital or reportedly had secondary infections in their study of 45 MIS-C patients followed up for nine months after discharge. This disparity was caused by the large number of patients in our study, as well as the fact that every patient with a history of fever was hospitalized to be monitored. Fever was the most common indication for rehospitalization in our study. Concomitant coronary involvement was assessed in one of the patients rehospitalized due to fever in terms of MIS-C reactivation. However, reactivation of MIS-C as the cause of the febrile state was ruled out since the fever was not persistent, the concomitant elevation of acute phase reactants was not observed, and troponin values of the patient with previous coronary involvement were within normal limits without any sequelae observed in the cardiac MRI.

While many studies have reported that cardiac symptoms usually resolve or normalize before discharge, some series have found that cardiac sequelae persist or that a coronary artery aneurysm develops after discharge.[11,12] Increased troponin levels and myocarditis were found in the pediatric patient group (mean age: 8±4 years) at a high rate of 60% in a study evaluating the cardiac outcomes of children with MIS-C.[13] Although the rates of MIS-C-associated myocarditis in our study were lower than in the literature, elevation of troponin was found in the postdischarge control of an 11-month-old patient whose cardiac enzymes remained normal during the first hospitalization but stayed at high levels for three weeks after discharge. Considering that there is limited information on long-term complications of MIS-C, the importance of long-term follow-up is emphasized in both our study and the literature.[14]

Posttraumatic pain syndrome has been linked to previous stress and trauma in the literature, and no MIS-C-related cases have been identified.[15] After excluding underlying systemic pathologies, our patient's pain and weakness were thought to be associated with previous intensive care hospitalization, which is consistent with the literature data.

Similar to the literature, in this study, hospitalized patients diagnosed with MIS-C had features overlapping with Kawasaki disease, such as the manifestation of cardiac and cutaneous involvement and conjunctivitis.[8,16] Based on these common characteristics, the possibility of reactivation should be considered in MIS-C patients, as is observed in Kawasaki disease.[17] However, while SARS-CoV-2 infection and its reactivation have been reported in adult studies, no evidence of MIS-C reactivation was found in the literature or in our study, and the causes of readmissions were not linked to MIS-C.[18]

Since MIS-C is a newly established disease, its long-term complications are unknown.[14] In the literature, published reports have mostly focused on its long-term cardiac effects.[8,10] In this report, the reasons for the rehospitalization of participants were analyzed to evaluate the long-term complications of MIS-C. One of the cases who did not regularly comply with the treatment protocol and had cardiac involvement in the active MIS-C period had a cardiac MRI performed for further investigation, but any MIS-C-related complications were not detected. As a result, according to MIS-C definitions, the causes and symptoms of readmission in the remaining patients did not meet the MIS-C criteria, and reactivation of MIS-C was not considered in any patient.

Several considerations should be noted when interpreting the results. This was a single-center retrospective study with inherent limitations compared to randomized clinical trials. However, 95 cases diagnosed with MIS-C in a single center should be considered a good sampling size, and the follow-up of the patients with the intention of readmission in case of need during the study after discharge makes the study valuable. While there are relevant studies in the

literature, including adult studies investigating readmissions after COVID-19, we could find few sources on readmissions in childhood, particularly after MIS-C. Therefore, it must be emphasized that the current study is the first report on rates and indications of readmissions among children who were previously diagnosed with MIS-C and followed up for a long-term after discharge.

In conclusion, fever may be a sign of infectious diseases in children as well as various noninfectious conditions. Furthermore, in children with a history of MIS-C, reactivation should be considered; thus, patients admitted with fever should be evaluated with close vital follow-up, clinical findings, cardiac imaging, and other examinations. Close follow-up of these patients is a must due to the possible cardiac complications of MIS-C.

Ethics Committee Approval: The study protocol was approved by the Dr. Behçet Uz Children's Training and Research Hospital Ethical Committee (decision: 2021, no: 17-11). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Were responsible for the idea/concept, design and analysis, and interpretation: E.C., İ.D., N.B.; Were responsible for data collection and processing: E.C., E.K., E.B., Ş.Ş., M.Y.Ç., M.G., A.A.K., T.M., H.A.; Was responsible for literature review, writing the article, critical review, references and funding, materials, and others: E.C.; Were responsible for control/supervision: İ.D., N.B.

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