





ORIGINAL ARTICLE

Multisystem inflammatory syndrome in children during severe acute respiratory syndrome coronavirus-2 pandemic in Turkey: A single-centre experience

Zeynep Savas Sen ¹, Gonul Tanir,¹ Ruveyda Gumuser Cinni,¹ Mutlu Uysal Yazici,² Tamer Yoldas,³ Zeynelabidin Ozturk ², Mete Han Kizilkaya,³ Suna Ozdem,¹ Rumeysa Yalcinkaya ¹, Caner Ozturk,⁴ Aslihan Yuce Sezen,⁴ Semanur Ozdel,⁵ Betul Emine Derinkuyu,⁶ Meltem Polat ¹ and Fatma Nur Oz¹

Departments of ¹Pediatric Infectious Disease, ²Division of Pediatric Intensive Care, ³Pediatric Cardiology, ⁴Ophthalmology, ⁵Pediatric Rheumatology, and ⁶Pediatric Radiology, SBU Ankara Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital, Ankara, Turkey

Aim: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection may result in a life-threatening hyperinflammatory condition named multisystem inflammatory syndrome in children (MIS-C). We aimed to assess demographics, clinical presentations, laboratory characteristics and treatment outcomes of patients with MIS-C.

Methods: We performed a retrospective study of patients with MIS-C managed between August 2020 and March 2021 at Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital in Turkey.

Results: A total of 45 patients (23 male, 51%) with a median age of 8.7 years (interquartile range: 5.6–11.7 years) were enrolled to study. The SARS-CoV-2 serology was positive in 43 (95%) patients. Organ-system involvement included the dermatologic in 41 (91%), cardiovascular in 39 (87%), hematologic in 36 (80%) and gastrointestinal in 36 (80%) patients. Acute anterior uveitis was diagnosed in nine (20%) patients. Two patients presented with clinical findings of deep neck infection such as fever, neck pain, trismus, swelling and induration on the cervical lymph node. One patient presented with Henoch–Schonlein purpura-like eruption. Coronary artery dilatation was detected in five (11%) patients. For treatment of MIS-C, intravenous immunoglobulin was used in 44 (98%) patients, methylprednisolone in 27 (60%) and anakinra in 9 (20%) patients. The median duration of hospitalisation was nine days. All patients recovered.

Conclusions: Children with MIS-C might have variable clinical presentations. Acute anterior uveitis might be a prominent presentation of MIS-C and require ophthalmological examination. It is essential to make patient-based decisions and apply a stepwise approach for the treatment of this life-threatening disease.

Key words: acute anterior uveitis; children; multisystem inflammatory syndrome associated with COVID-19; SARS-CoV-2.

What is already known on this topic

- Multisystem inflammatory syndrome in children (MIS-C) is a rare and severe complication of coronavirus disease 2019 (COVID-19).
- The clinical spectrum of MIS-C ranges from mild, self-limited disease to severe systemic inflammation and multisystem organ involvement.
- The recommended treatment strategy includes intravenous immunoglobulin alone or in combination with corticosteroids and other biological agents.

What this paper adds

- Children with multisystem inflammatory syndrome may have variable presentations such as deep neck infection, Henoch–Schonlein purpura-like rash.
- Acute anterior uveitis might be a prominent presentation of the multisystem inflammatory syndrome in children and require ophthalmological examination.
- It is essential to make patient-based decisions and apply a stepwise approach to treat multisystem inflammatory syndrome in children.

Correspondence: Dr Zeynep Savas Sen, SBU Ankara Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital, Department of Pediatric Infectious Disease, 06080 Altındağ, Ankara, Turkey. Fax: +90 3123170353; email: zeysa81@gmail.com

Conflict of interest: None declared.

Accepted for publication 15 July 2021.

The clinical course of paediatric coronavirus disease 2019 (COVID-19) has a broad spectrum ranging from asymptomatic infection to critical illness.¹ In children, COVID-19 can cause a rare but life-threatening hyperinflammatory syndrome which was named multisystem inflammatory syndrome in children (MIS-C) by the CDC in May 2020.^{2,3} Children with MIS-C can develop clinical features resembling other inflammatory conditions such as macrophage activation syndrome, Kawasaki shock syndrome and toxic shock syndrome.¹ This life-threatening

syndrome requires aggressive management. The disease can be controlled, and end-organ damage can be prevented by timely initiating appropriate therapies.⁴ However, the clinical spectrum and optimal treatment regimens for MIS-C have not been fully described yet. This study aimed to assess demographics, clinical presentations, laboratory characteristics and treatment outcomes of patients with MIS-C.

Materials and Methods

We conducted a single-centre retrospective study on patients with MIS-C managed between August 2020 and March 2021 at the Pediatric Infectious Disease Department of Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital in Turkey. Patients were diagnosed with MIS-C according to CDC case definition criteria.³ Demographic information, laboratory parameters, echocardiographic, radiological findings and treatment modalities were recorded.

We described organ/system involvement according to the symptoms, clinical, laboratory and radiological findings. Gastrointestinal system (GIS) involvement was assessed based on the presence of diarrhoea, vomiting, abdominal pain and elevated liver function tests. Cardiac involvement included coronary artery anomalies and/or valvular regurgitation, myocarditis, and pericardial effusion. Clinical myocarditis was defined as the presence of cardiac dysfunction on echocardiography with elevated troponin-I (>0.039 ng/mL) and/or pro-brain-type natriuretic peptide (pro-BNP) (>93 pg/mL) levels. Left ventricular (LV) dysfunction was defined as an LV ejection fraction (LVEF) of <55% based on Boston Z-scores. Dilatation of a coronary artery was defined by Z-scores.⁵ Neurologic involvement was determined by the presence of lethargy, confusion, irritability, encephalopathy, seizures, meningoencephalitis, muscle weakness and brain-stem and/or cerebellar signs. Hematologic involvement was defined as neutrophilia, lymphopenia and/or thrombocytopenia. Acute kidney injury was characterised by a creatinine level higher than the upper limit for age. Ophthalmological examination with slit lamp was performed in patients with persistent redness of the eye, blurred vision, photophobia and eye pain either at admission or during follow-up.

Nasopharyngeal swab tests for reverse transcription-polymerised chain reaction (RT-PCR) for SARS-CoV-2 were performed in the Republic of Turkey Ministry of Health General Directorate of Public Health laboratories. SARS-CoV-2 total antibodies (Immunoglobulin (Ig) M and IgG) were measured using Siemens Healthineers Centaur XPT system, Germany.

Chest radiography was performed on all patients. Abdominal ultrasonography (USG) and/or computed tomography (CT) and cranial magnetic resonance imaging were also performed in patients with indication.

The treatment modalities were also recorded. Firstly, intravenous immunoglobulin (IVIG) (2 g/kg) was administered in a single infusion over 12 h. If there was a concern that the patient will not tolerate the single-dose volume load, it was given in divided doses over two days. Glucocorticoid therapy (methylprednisolone 2 mg/kg/day (max of 60 mg per day)) was commenced in patients with persistent fever and rising inflammatory markers despite treatment with IVIG. In life-threatening circumstances like severe or refractory shock, high doses of methylprednisolone and recombinant interleukin-1 (IL-1) receptor antagonist (anakinra, range: 2–10 mg/kg/dose (max

100 mg/dose) q12h) were used in a stepwise approach. Empiric antibiotic therapy was given to all patients. Antiviral drugs were not used in any patients. Aspirin and/or low molecular weight heparin (LMWH) were administered to patients with significantly elevated D-dimer levels, severe MIS-C manifestations requiring paediatric intensive care unit (PICU) admission, LV dysfunction, coronary artery dilatation or aneurysm. Paediatric risk of mortality score III (PRISM III) and paediatric logistic organ dysfunction score 2 (PELOD-2) were calculated in patients admitted to the PICU.⁶

Ethics committee approval was received from Dr. Sami Ulus Maternity Child Health and Diseases Training and Research Hospital Ethics Committee (2020, No: E-20/12-44).

Statistical analysis

Data were entered into a database that was analysed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). Descriptive analysis was used to characterise the patients. Pearson's χ^2 test or Fisher's exact test was used for between-group comparisons. Values are shown as a median and interquartile range for data not normally distributed. The

Table 1 The demographic and clinical characteristics of patients diagnosed with MIS-C

Characteristics	Total (n = 45)
Demographic characteristics	
Median age (min–max, years)	8.7 (2.06–14.8)
Male, n (%)	23 (51.1)
Symptoms at admission, n (%)	
Constitutional	
Fever	45 (100)
Dermatologic	
Rash	26 (57.8)
Conjunctivitis	41 (91.1)
Lymphadenopathy	7 (15.6)
Respiratory	
Sore throat	7 (15.6)
Cough	9 (20)
Cardiovascular	
Chest pain	3 (6.6)
Gastrointestinal	
Vomiting	20 (44.4)
Diarrhoea	18 (40)
Abdominal pain	23 (51.1)
Renal	
Haematuria	1 (2.2)
Neurological	
Headache	5 (11.1)
Altered consciousness	4 (9.1)
Recent or current SARS-CoV-2 infection or exposure, n (%)	
COVID-19 exposure history	29 (64.4)
Positive SARS-CoV-2 RT-PCR	4 (8.8)
Positive SARS-CoV-2 serology	43 (95.5)

RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

nonparametric Mann–Whitney *U* test was used to compare medians for unpaired comparisons and the Wilcoxon test for paired comparisons. The Kruskal–Wallis test was used to compare medians among the different groups. Differences were considered significant at *P* values of 0.05.

Results

A total of 45 children who were diagnosed with MIS-C were enrolled to study. The median age was 8.7 years (interquartile range (IQR): 5.6–11.7 years) and 23 (51%) of the patients were male. There was no patient under 12 months of age. Five patients were toddlers (<3 years). Most patients were previously healthy, except three (6.6%) overweight patients. The median duration of fever before hospitalisation was five days (IQR: 4–6 days). The most common presenting symptoms were conjunctival injection in 41 (91%) patients and gastrointestinal (GI) complaints in 36 (80%). Eleven (24%) patients were admitted to the PICU. The demographic and clinical characteristics of patients are shown in Table 1.

One patient presented with purpuric rash and seven days of fever, conjunctivitis, cough and sore throat. Although MIS-C was considered in the preliminary diagnosis with these findings, a skin biopsy was performed for the differential diagnosis. The histopathological analysis revealed leukocytoclastic vasculitis. She had no abdominal pain, arthritis, arthralgia or renal involvement and strongly positive for COVID-19 IgG. Therefore, she was diagnosed as MIS-C presenting as Henoch–Schönlein purpura (HSP)-like eruption and treated successfully with IVIG and

corticosteroid. Two patients presented with clinical findings of deep neck infection such as fever, neck pain, trismus, swelling and induration on the cervical lymph node. The patients were subsequently diagnosed with MIS-C because of abdominal tenderness, conjunctivitis, persistent fever and rising inflammatory markers despite antibiotic treatment.

Hyponatremia, lymphopenia, hypoalbuminemia, thrombocytopenia and anaemia were detected in 35 (78%), 31 (69%), 18 (40%), 15 (33%) and 9 (20%) of the patients respectively. Nineteen (42%) patients had highly elevated ferritin levels (>500 ng/mL). Forty-two (93%) of the patients had high serum pro-BNP, and 22 (49%) had high troponin-I levels. Table 2 shows the laboratory findings of patients with and without PICU admission.

Immunoglobulin G antibodies against SARS-CoV-2 were positive in 43 (96%) patients. Four (9%) patients with MIS-C had a positive SARS-CoV-2 RT-PCR test. Twenty nine of 45 (64%) patients had a history of exposure to a confirmed COVID-19 case within a median of 4 weeks (range: 1–6 weeks) before the onset of the symptoms.

Organ-system involvement included as the dermatologic in 41 (91%), cardiovascular in 39 (87%), hematologic in 36 (80%), GIS in 36 (80%), renal in 15 (33%), respiratory in 11 (24%) and neurological in 8 (18%) patients. Acute anterior uveitis (AAU) was detected in 9 of 29 patients who had an ophthalmologic examination. There was no significant difference regarding the age, gender and presenting symptoms between the patients with or without AAU. However; procalcitonin, fibrinogen, ferritin and pro-BNP levels were significantly higher in patients with AAU than patients without AAU. Table 3 shows the clinical, laboratory

Table 2 Laboratory findings of patients with or without PICU admission

Laboratory findings*	Total (n = 45)	PICU-patient (n = 11)	Non-PICU patient (n = 34)	<i>P</i>
WBC, ×10 ³ /μL	9.8 (7–14)	13 (8–15)	9 (7–14)	0.191
ANC, ×10 ³ /μL	7 (5.4–12.6)	11.6 (7–13)	6.7 (5–11.3)	0.081
ALC, ×10 ³ /μL	0.9 (0.66–1.6)	0.72 (0.6–0.9)	1.02 (0.67–1.7)	0.041
Haemoglobin, g/dL	12 (11–13)	11.3 (10.8–12.4)	12 (11–13)	0.113
PLT, ×10 ⁹ /μL	188 (133–251)	148 (93–308)	190 (140–235)	0.616
CRP, mg/L	145 (108–196)	174 (116–298)	143 (103–182)	0.088
Procalcitonin, ng/mL	4.8 (2–12)	12 (3.4–85)	5 (1.6–10)	0.045
Interleukin-6, pg/mL	173 (64–446)	750 (630–2130)	183 (62–371)	0.792
ESR, mm/h	46 (30–59)	58 (40–73)	40 (26–56)	0.048
Fibrinogen, mg/dL	491 (420–611)	548 (418–697)	474 (416–610)	0.35
Ferritin, ng/mL	405 (212–978)	750 (630–2130)	341 (183–681)	0.005
Triglyceride, mg/dL	209 (156–274)	219 (205–306)	188 (133–274)	0.198
D-dimer, ng/mL	4044 (2081–6154)	5649 (2969–15 814)	3660 (1896–5426)	0.044
Sodium, mmol/L	132 (129–134)	133 (130–135)	131.5 (129–133)	0.236
Albumin, g/dL	3.3 (2.9–3.7)	2.9 (2.7–3.3)	3.5 (3–3.8)	0.002
Creatinine, mg/dL	0.64 (0.52–0.82)	1 (0.66–1.12)	0.59 (0.5–0.7)	0.005
AST, IU/L	38 (27–75)	73 (27–140)	37 (27–61)	0.129
ALT, IU/L	30 (15–58)	66 (20–91)	27 (15–52)	0.091
LDH, IU/L	298 (258–360)	332 (249–588)	298 (267–337)	0.303
Troponin, ng/mL	0.05 (0.015–0.19)	0.11 (0.03–1.04)	0.03 (0–0.13)	0.027
Pro-BNP, pg/mL	4340 (1092–11 374)	12 675 (4811–35 000)	2137 (768–9497)	0.006

*Values are median (interquartile ranges). Statically significant datas (*p*<0.05) were highlighted in bold-italic. ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; PICU, paediatric intensive care unit; PLT, platelet; pro-BNP, pro-brain natriuretic peptide; WBC, white blood cell.

findings and treatments of the patients with and without uveitis. The slit-lamp examination of 12-year-old boy who had bilateral conjunctivitis at admission and blurred vision on the 10th day of his hospitalisation is shown in Figure 1.

Chest radiography was normal in 21 (47%) patients. Interstitial infiltration and ground-glass opacity were detected in 6 (13%) and 2 (4%) patients, respectively. Sixteen (36%) patients had pleural effusion, and six of them were bilateral. Abdominal USG was performed in 40 patients. The most common findings were free fluid in 14 (35%) patients, mesenteric lymphadenopathy in 8 (20%), bowel wall thickening/oedema in 7 (18%), hepatosplenomegaly in 8 (20%), and gallbladder hydrops in 5 (13%). Abdominal CT was performed in eight (18%) patients and revealed mesenteric lymphadenopathy, hepatomegaly and ileitis in six, four and two patients, respectively.

Echocardiography was performed on all patients at admission. Mitral valve regurgitation was detected in 30 (67%) patients, myocarditis in 23 (51%), LV dysfunction in 8 (18%) and coronary artery dilatation in 5 (11%) patients.

Forty four (98%) patients were treated with high dose IVIG on the median 6 (range: 3–10) days of fever. Seventeen (38%) patients were given IVIG alone, and 27 (60%) patients received concomitant methylprednisolone. One patient did not receive

any treatment because of a mild disease course. Anakinra was commenced on nine (20%) patients and six of them were admitted to the PICU. Procalcitonin, interleukin-6, prothrombin time, international normalised ratio (INR), D-dimer, ferritin, pro-BNP, creatinine, aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase values were significantly higher ($P < 0.05$) in patients who received anakinra treatment than patients who did not receive; however, albumin and platelet levels were significantly lower ($P < 0.05$).

A total of 17 (38%) patients received aspirin alone, 13 (29%) received LMWH alone and 1 (2%) received both. No thrombotic event was detected.

The clinical characteristics of 11 (24%) patients admitted to the PICU are summarised in Table 4.

Discussion

This study showed that children with MIS-C might present with variable clinical presentations, and AAU might be a prominent finding of MIS-C. The most common presenting symptoms were conjunctival injection and GI manifestations. Although the number of AAU patients was limited, we found that patients with AAU had significantly higher procalcitonin, fibrinogen, ferritin

Table 3 Clinical and laboratory features and treatment modalities of patients with and without anterior uveitis

	AAU (+) (n = 9)	AAU (-) (n = 20)	P value
Time to ophthalmologic examination, median (min–max) day*	3 (2–11)	3 (1–7)	0.489
Organ-system involvement, n (%)			
Cardiovascular	9 (100)	17 (85)	0.532
Respiratory	1 (11.1)	3 (15)	1
Renal	5 (55.5)	4 (20)	0.088
Neurologic	3 (33.3)	3 (15)	0.339
Hematologic	8 (88.8)	16 (80)	1
Gastrointestinal	9 (100)	13 (65)	0.066
Dermatologic	5 (55.5)	11 (55)	1
Laboratory findings, median (interquartile ranges)			
WBC, $\times 10^3/\mu\text{L}$	11.6 (7.4–14)	8.66 (6.4–11.7)	0.3
ALC, $\times 10^3/\mu\text{L}$	0.73 (0.64–0.87)	0.93 (0.65–1.6)	0.358
CRP, mg/L	168 (126–247)	132 (97.5–166)	0.066
ESR, mm/h	58 (52–70)	46 (31–59.2)	0.077
Interleukin-6, pg/mL	648 (494–1922)	212.7 (142–389)	0.869
Procalcitonin, ng/mL	10 (3.5–55.5)	2.8 (1.12–9.06)	0.037
Fibrinogen, mg/dL	619 (547–732)	466 (409–596)	0.004
D-dimer, ng/mL	4382 (3341–6477)	2767 (1631–4950)	0.12
Ferritin, ng/mL	648 (494–1922)	212 (142–389)	0.006
Albumin, g/dL	3 (2.8–3.35)	3.6 (3.5–3.8)	0.004
Troponin, ng/mL	0.11 (0.035–0.3)	0.025 (0–0.13)	0.095
Pro-BNP, pg/mL	14 725 (5688–28 135)	1416 (679–6536)	0.01
Treatment, n (%)			
IVIG only	2 (22.2)	9 (45)	0.412
IVIG + methylprednisolone	4 (44.4)	8 (40)	1
IVIG + methylprednisolone + anakinra	3 (33.3)	3 (15)	0.339

*Time from the first day of fever to ophthalmologic examination. Statically significant datas ($p < 0.05$) were highlighted in bold-italic. ALC, absolute lymphocyte count; AAU, acute anterior uveitis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; pro-BNP, pro-brain natriuretic peptide; WBC, white blood cell.

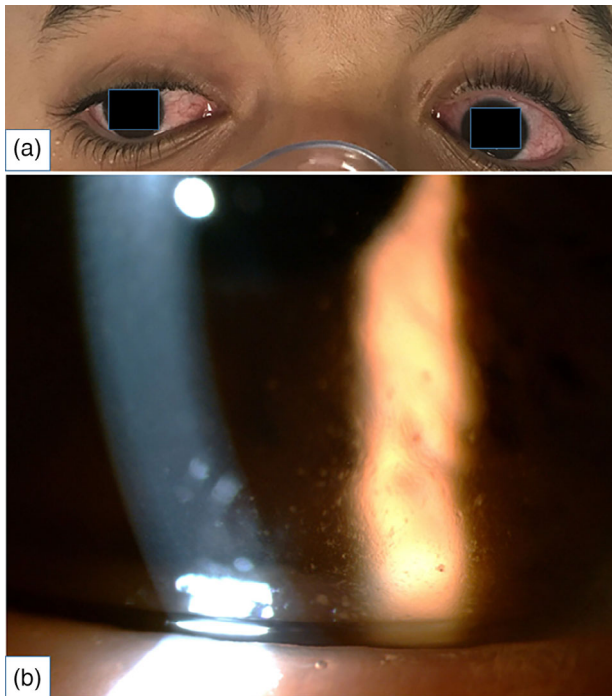


Fig. 1 (a) Bilateral conjunctivitis (b) Descemet's membrane folds and small, round, white keratic precipitates in Arlt's triangle by slit-lamp examination.

and pro-BNP levels. In patients who required PICU care, cardiac involvement was common, and ferritin, troponin, pro-BNP, ESR, procalcitonin, D-dimer and creatinine levels were significantly higher than those without PICU admission. Approximately 38% of our patients recovered with IVIG treatment alone. Anakinra was commenced in 20% of the patients because of a lack of adequate clinical response to previous treatments with IVIG and methylprednisolone. All of our patients had a favourable course.

MIS-C has been reported in clusters 2–6 weeks after the acute infection in areas with a high COVID-19 disease burden.^{5–7} The first case of SARS-CoV-2 was detected in March 2020 in Turkey. Patients with MIS-C started to be treated in our hospital in August 2020. In the present study, 64% of patients had family members with SARS-CoV-2 RT-PCR positivity four weeks before, on average. The demographic characteristics of children with MIS-C are still limited and evolving daily. However, in most studies, the patients were usually previously healthy, slightly more frequently in male patients and aged between 8 and 11 years and, as in our study.^{8,9}

Anterior uveitis is an intraocular inflammation featuring the anterior chamber as the predominant site of inflammation. Various pathogens affecting the GI, urinary and respiratory tracts were reported as triggers of intraocular inflammation.¹⁰ Anterior uveitis also is an ophthalmological finding in Kawasaki disease (KD). Previous studies have shown that acute uveitis was seen in about 20–80% of the KD patients.^{11,12} It has been reported that the presence of AAU was significantly correlated with a higher neutrophil count, higher CRP levels and coronary artery

dilatation in 36 patients with KD.¹¹ In the present study, AAU was diagnosed in 20% of the patients, and acute phase reactants, ferritin and pro-BNP were significantly high in AAU patients than those without AAU. The timing and criteria of ophthalmologic examination should also be investigated in further studies.

COVID-19-related IgA vasculitis cases were reported during the pandemic. A 3-year-old male diagnosed with HSP based on clinical criteria had positive SARS-Cov-2 PCR, and positive COVID-19 IgA was reported. The authors declared that this is the first paediatric case of classic HSP in the setting of COVID-19 infection.¹³ In our study, a 12-year-old female patient with MIS-C presented with an HSP-like rash. Leukocytoclastic vasculitis was determined by skin biopsy. HSP was not considered due to other findings meeting MIS-C criteria. She was treated successfully with IVIG and corticosteroid.

A study of 186 patients with MIS-C from US lymphadenopathy was reported in 18 (10%) patients.¹⁴ In a systemic review, which included 655 MIS-C patients, cervical lymphadenitis was reported in 4% of the patients.¹⁵ Daube *et al.* reported three children with suspected MIS-C found to have retropharyngeal oedema.¹⁶ Han *et al.* reported a 15-year-old-boy with neck pain and stiffness. Retropharyngeal fluid was detected in his neck CT. COVID-19 serology was positive and he was treated with IVIG and steroids.¹⁷ In our study, two patients presented with signs of deep neck infection. The history of COVID-19 exposure and COVID-19 serology was positive. No clear evidence of bacterial infection was identified. We diagnosed MIS-C with other clinical findings such as fever, abdominal tenderness and conjunctivitis. All signs and laboratory parameters were resolved after IVIG and steroid treatment.

The aetiology of cardiovascular involvement in MIS-C is considered to be multifactorial. Cardiac involvement often occurs in LV dysfunction, coronary artery dilatation/aneurysm, and electrical conduction abnormalities.^{4,18} Kaushik *et al.* reported LV dysfunction in 43.7% of patients, myocarditis in 23% of patients and coronary artery dilatation/aneurysm in 23.4% of patients.¹⁵ In our study, valvular dysfunction was the most common cardiac involvement, followed by myocarditis and LV dysfunction. Coronary artery dilatation was rare and only detected in five patients.

Although MIS-C is clinically similar to KD, the distinguishing characteristics from KD are GI symptoms' common occurrence and older patients being affected in age group.^{2,19} Nakra *et al.* reported that a few children were operated on due to GI symptoms. Mesenteric lymphadenopathy and peritonitis were found intraoperatively.² In the present study, seven (16%) patients were consulted with paediatric surgery for the acute abdomen, but none had exploratory laparotomy. The USG and CT imaging in patients with significant GI findings might be helpful.

Changes in consciousness may be observed in MIS-C cases; severe encephalopathy or focal brain lesions have been reported rarely. Six MIS-C were reported in a case series, and four (66.6%) had neurological symptoms; one had diffuse cerebral oedema on CT. This was attributed to the underlying inflammatory event, the pathogenesis of which could not be fully explained.²⁰ In our study, four patients had altered consciousness on admission. Diffusion restriction in the corpus callosum splenium with T2 and FLAIR hyperintensity ultimately resolved after two weeks were detected in one patient. Little is known about the short- and long-term consequences of focal brain lesions.

Table 4 The characteristics of patients admitted to the paediatric intensive care unit

No	Sex	Age, year	History of contact with a COVID-19 case	Symptoms prior to PICU admission	Duration of fever, day	Clinical findings at PICU admission	PRISM III, PELOD-2	Ejection fraction at admission, %	Supportive treatments	Treatment	Length of PICU stay, days
1	F	10.6	Unknown	Fever, abdominal, chest pain, lethargy	4	Shock, ARDS, ACD, ALD, AKI, EP	36, 32	38	VD, IMV, TPE, CVVHDF	IVIG, CS, Anakinra, BSA, LMWH	10
2	M	13.5	Household	Fever, abdominal pain, lethargy	3	Shock, ACD, ALD, AKI, EP	14, 10	69	VD, FFO, FFP	IVIG, CS, Anakinra, BSA, LMWH	11
3	F	2.3	Household	Fever, diarrhoea	5	Shock, ACD, ALD, AKI	40, 32	45	VD, IMV, TPE, CVVHDF	IVIG, CS, Anakinra, BSA, LMWH	15
4	M	12.6	Household	Fever	5	Shock, ACD, ALD	9, 20	63	VD, FFO, FFP	IVIG, CS, BSA, LMWH, ASA	3
5	M	8.2	Household	Fever, vomiting	6	Shock, ACD	14, 10	60	VD, FFO	IVIG, CS, BSA, LMWH	3
6	F	9.3	Unknown	Fever, vomiting, diarrhoea, abdominal pain, lethargy	2	ACD, ALD, EP	15, 10	63	VD, FFO, FFP	IVIG, CS, Anakinra, BSA, LMWH	6
7	M	6.2	Household	Fever, headache, abdominal pain,	7	Shock, ACD	12, 10	54	VD, FFO	IVIG, CS, BSA, LMWH	2
8	F	14.5	Household	Fever, headache, lethargy	7	Shock, ACD, ALD, AKI, EP	44, 41	20	VD, IMV, TPE, CVVHDF	IVIG, CS, Anakinra, BSA, LMWH	10
9	M	14.8	Household	Fever, headache, abdominal pain	7	ACD, AKI	16, 12	55	HFNC, CS	IVIG, CS, Anakinra, BSA, LMWH	5
10	F	11.7	Household	Fever, diarrhoea	5	Shock, ACD	26, 16	66	VD, CS	IVIG, CS, BSA, LMWH	3
11	M	8.7	Household	Fever, vomiting, diarrhoea	7	ACD	12, 11	68	CS, FFO	IVIG, CS, BSA, LMWH	3

ACD, acute cardiac dysfunction; AKI, acute kidney injury; ALD, acute liver dysfunction; ARDS, acute respiratory distress syndrome; ASA, acetylsalicylic acid; BSA, broad spectrum antibiotic; CAD, coronary artery dilatation; CS, corticosteroid; CVVHDF, continuous venovenous haemodiafiltration; EP, encephalopathy; FFO, free flow oxygen; FFP, fresh frozen plasma; HFNC, high flow nasal cannula; IMV, invasive mechanical ventilation; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; PELOD-2, paediatric logistic organ dysfunction score 2; PRISM III, paediatric risk of mortality score III; TPE, therapeutic plasma exchange; VD, vasoactive drugs.

The inflammatory markers are not specific to MIS-C.¹⁹ Elevated CRP levels, IL-6 and procalcitonin might be associated with multi-organ damage.^{18,21} Elevated BNP/pro-BNP can help differentiate between patients with and without LV dysfunction. In

particular, BNP is an acute phase reactant and an indicator of inflammation.¹⁸ In our study, CRP, IL-6, ferritin and D-dimer values were high in all patients as evidence of cytokine storm. We also found that serum procalcitonin, ESR, ferritin, D-dimer,

creatinine, troponin-I and pro-BNP levels were higher in patients admitted to PICU.

Recommended treatment strategies were IVIG that can be used alone or in combination with corticosteroids in MIS-C.^{5,6} Treatment with anakinra and other biological agents has been suggested in cases resistant to IVIG and/or corticosteroid therapy.^{4,5} In our study, approximately 38% of our patients recovered with IVIG therapy alone. Corticosteroid was given to patients who did not respond to IVIG. Anakinra was commenced in 20% of critically ill patients and unresponsive to IVIG and corticosteroid treatment. According to the patient's clinical condition and response to first-line therapies within 24–36 h, we suggest initiating anakinra treatment in a stepwise manner without delay. The rate of anticoagulant use in the MIS-C case series is highly variable, at 12.5–90.1%.²² Our study considered the high levels of D-dimer and cardiac dysfunction findings; we started acetylsalicylic acid alone in 38% of patients and LMWH in 31% of patients. We observed no thrombotic event such as embolism or stroke, similar to the other studies.⁵

This study has some limitations, such as low sample size, including data of a single-centre and retrospective nature.

In conclusion, we report an experience with different clinical manifestations of MIS-C. Clinical picture mimicking deep neck infection and HSP-like rash were exciting presentations that we determined. The stepwise treatment approach of initiating immunomodulatory drugs was found successful in the present study. AAU was a notable MIS-C finding in this study. Although our numbers are small and more studies are needed to verify AAU as MIS-C criteria, ophthalmologic examination to all patients with MIS-C might be considered.

Acknowledgement

The authors thank to nurses and other health-care professionals who work in the department of paediatric infectious diseases and paediatric intensive care unit.

References

- Pereira MFB, Litvinov N, Farhat SCL et al. Severe clinical spectrum with high mortality in pediatric patients with COVID-19 and multisystem inflammatory syndrome. *Clinics* 2020; **75**: e2209. <https://doi.org/10.6061/clinics/2020/e2209>.
- Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multisystem inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: Review of clinical presentation, hypothetical pathogenesis, and proposed management. *Children* 2020; **7**: 69. <https://doi.org/10.3390/children7070069>.
- Network CDC. *Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)*; 2020. Available from: <https://emergency.cdc.gov/han/2020/han00432.asp>
- Lee PY, Day-Lewis M, Henderson LA et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. *J. Clin. Invest.* 2020; **130**: 5942–50.
- Capone CA, Subramony A, Sweberg T et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. *J. Pediatr.* 2020; **224**: 141–5.
- Dufort EM, Koumans EH, Chow EJ et al. Multisystem inflammatory syndrome in children in New York State. *N. Engl. J. Med.* 2020; **383**: 347–58.
- Elias MD, McCrindle BW, Larios G et al. Management of Multisystem Inflammatory Syndrome in children associated with COVID-19: A survey from the International Kawasaki Disease Registry. *CJC Open* 2020; **2**: 632–40.
- McCrindle BW, Rowley AH, Newburger JW et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation* 2017; **135**: e927–99.
- Gonçalves JP, Severo M, Rocha C, Jardim J, Mota T, Ribeiro A. Performance of PRISM III and PELOD-2 scores in a pediatric intensive care unit. *Eur. J. Pediatr.* 2015; **174**: 1305–10.
- Lee OL. Idiopathic and other anterior uveitis syndromes. In: Yanoff M, Duker JS, eds. *Ophthalmology*, 5th edn. Philadelphia, PA: Elsevier; 2019; 773–6.
- Choi HS, Lee SB, Kwon JH, Kim HS, Sohn S, Hong YM. Uveitis as an important ocular sign to help early diagnosis in Kawasaki disease. *Korean J. Pediatr.* 2015; **58**: 374–9.
- Ohno S, Miyajima T, Higuchi M et al. Ocular manifestations of Kawasaki's disease (mucocutaneous lymph node syndrome). *Am. J. Ophthalmol.* 1982; **93**: 713–7.
- Jacobi M, Lancrei HM, Brosh-Nissimov T, Yeshayahu Y. Purpurona: A novel report of COVID-19-related Henoch-Schönlein Purpura in a child. *Pediatr. Infect. Dis. J.* 2021; **40**: e93–4.
- Feldstein LR, Rose EB, Horwitz SM et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N. Engl. J. Med.* 2020; **383**: 334–46.
- Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. *Pediatr. Infect. Dis. J.* 2020; **39**: e340–6.
- Daube A, Rickert S, Madan RP, Kahn P, Rispoli J, Dapul H. Multisystem inflammatory syndrome in children (MIS-C) and retropharyngeal edema: A case series. *Int. J. Pediatr. Otorhinolaryngol.* 2021; **144**: 110667.
- Han P, Douillard J, Cheng J, Ramanathan A, Tieu D, Degner T. Multisystem inflammatory syndrome in children in a 15-year-old male with a retropharyngeal phlegmon. *Case Rep. Pediatr.* 2020; 6668371. <https://doi.org/10.1155/2020/6668371>.
- Henderson LA, Canna SW, Friedman KG et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and Hyperinflammation in pediatric COVID-19: Version 1. *Arthritis Rheumatol.* 2020; **72**: 1791–805.
- Radia T, Williams N, Agrawal P et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. *Paediatr. Respir. Rev.* 2020; **38**: 51–7.
- Chiotos K, Bassiri H, Behrens EM et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: A case series. *J. Pediatric Infect. Dis. Soc.* 2020; **9**: 393–8.
- Toubiana J, Poirault C, Corsia A et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: Prospective observational study. *BMJ* 2020; **369**: m2094.
- Simon Junior H, Sakano TMS, Rodrigues RM et al. Multisystem inflammatory syndrome associated with COVID-19 from the pediatric emergency physician's point of view. *J. Pediatr.* 2020; **97**: 140–59.