

Multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 infection in the state of Qatar: Association with Kawasaki-like Illness

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Abstract. *Introduction:* World Health Organization (WHO) is encouraging reporting of children with Multisystem Inflammatory Syndrome (MIS-C) associated with SARS-CoV-2 infection for better understanding and management of the disease. *Methodology:* This retrospective study included the first 15 pediatric patients with a confirmed diagnosis of MIS-C associated with SARS-CoV-2 infection in the state of Qatar. We studied and analyzed their demographic data, clinical manifestations, laboratory tests, treatment, and outcome. *Results:* A total of 15 children were studied (mean age 3.5 ± 2.7 year). Recent severe acute respiratory syndrome coronavirus 2 infection was identified in all of them (100%). The majority of these patients had 4 or more systems involvement. Nine of the 15 presented with Kawasaki disease - picture and all had gastrointestinal symptoms (vomiting and diarrhea). Five required Pediatrics Intensive Care Unit (PICU) admission. Lab investigations revealed high D-Dimer, hyponatremia, and hypoalbuminemia in all. Low hemoglobin (Hb), thrombocytopenia, and sterile pyuria occurred in 86.6%, 60% and 75% of them, respectively. Treatment with combined anti-inflammatory medications (intravenous immunoglobulin, corticosteroids) was used in along with immunomodulatory agents (Anakinra) in a selected group of refractory patients. No mortality happened. *Conclusion:* Our young children who presented with MIS-C related to SARS-CoV-2 infection had significantly higher Kawasaki-disease picture compared to other reports. One third of them required PICU admission but no mortality occurred. (www.actabiomedica.it)

Key word: SARS-CoV-2 infection, Multisystem Inflammatory Syndrome (MIS-C), infants, children, treatment, Qatar.

Introduction

Qatar is one of over 200 countries reported to be affected by the COVID-19 pandemic, with a current prevalence of the disease affecting more than 100,000 inhabitants (1). Children and adolescents

are reported to experience fewer symptoms of the acute virus infection compared to adults. However, there are increasing number of reports of SARS-CoV-2 infection-related complications, including multisystem inflammatory syndrome in children (MIS-C).

MIS-C associated with COVID-19 infection was described in children who presented with persistent fever, a hyper-inflammatory state, and multiorgan involvement in the United Kingdom (UK) and the United States (2,3). Although not all MIS-C patients were SARS-CoV-2 positive as some of them had negative real time polymerase chain reaction (RT-PCR) results, they had been strongly exposed to confirmed cases of SARS-CoV-2 infection or had a positive antibody titer to the virus (2).

Herein, we describe clinical characteristics, laboratory findings, management, and outcomes in 15 children below the age of 14 years of age who were admitted to our facility with MIS-C in the State of Qatar. The diagnosis of MIS-C was based on the WHO definition, Center for Disease Control and Prevention (CDC-USA) guidelines, and guidelines from the Royal College of Pediatrics and Child Health (RCPCH-UK) and included clinical and laboratory evidence of persistent fever along with a hyper-inflammation state and multi-organ involvement (2, 4, 5).

Methods

We performed a retrospective study on all patients (aged 0–14 years) admitted to the pediatric unit between March 1, 2020, and July 31, 2020, with suspected MIS-C associated with SARS-CoV-2 infection.

According to the definition by the Centers for Disease Control and Prevention (CDC-USA), the cases described here were defined as follows (6) (Table 1).

We collected demographic characteristics, including comorbidities, clinical manifestations, laboratory data, echocardiogram findings, imaging data, treatment used and disease outcomes.

Laboratory investigation results included a complete blood count (CBC) and a differential count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, D-dimer, renal function, electrolytes, liver function, serum ferritin, lactate dehydrogenase (LDH), interleukin 6 (IL-6), interleukin 2 (IL-2) (in selected patients), triglycerides, troponin, pro-B-type natriuretic peptide (Pro-BNP), 25-hydroxyvitamin D3, and albumin. Blood and urine samples were collected on admission.

We also addressed Kawasaki disease symptoms (mucocutaneous manifestations including bilateral bulbar non-purulent conjunctivitis, oral mucosal changes,

Table 1. CDC case definition (from ref. 6)

All 4 criteria must be met:
1. Age <21 years
2. Clinical presentation of MIS-C, including:
• Fever: equal or > to 24 h
• Laboratory evidence of inflammation
• Multisystem involvement equal or > to 2 organ systems
• Severe illness requiring hospitalization
3. No alternative plausible diagnosis
4. Evidence of recent SARS-CoV-2 infection/exposure:
• Positive SARS-CoV-2 (RT-PCR)
• Positive serology
• Positive antigen test
• COVID-19 exposure within 4 weeks prior to the onset of symptoms

oedema, skin peeling of fingers, rash, and unilateral cervical lymphadenopathy) among patients with the MIS-C syndrome. The requirement and duration of Pediatric Intensive Care Unit (PICU) admission, respiratory support requirements, and clinical outcomes were recorded.

Patients were labelled with cardiac involvement if their laboratory tests indicated evidence of myocardial injury (elevated troponin level or elevated Pro-BNP level), or had echocardiogram abnormalities, or presented shock requiring inotropic support.

Patients who met the MIS-C definition were treated with high-dose intravenous immunoglobulin (IVIG), glucocorticoids, and acetylsalicylic acid (ASA), while immunomodulatory therapy with Anakinra (interleukin 1 receptor antagonist) was given to patients with clinical decompensation and/or to those who did not respond to IVIG and glucocorticoids.

According to our local protocol, if thrombosis was not detected, therapeutic dose of enoxaparin was not initiated; however, patients admitted to the PICU were treated with enoxaparin prophylaxis for 2 weeks. Other indications for starting prophylaxis anticoagulation (7) were any of the following:

- D- Dimer >2 mcg/ml
- Central venous catheter
- Obesity
- History of thrombosis/thrombophilia.

- Congenital/acquired heart disease with venous stasis or cardiac rhythm abnormalities
- Mechanical ventilation.

Moreover, indication of starting treatment with anti-coagulation included (7):

- Documented venous thromboembolism (VTE).
- Moderate to severe cardiac ventricular dysfunction.
- Coronary aneurysm >10 Z score.
- Expert opinion in the situation of multiple risk factors

Low-dose aspirin was started once MIS-C was diagnosed unless there was a low platelet count (<80,000 μ L). Aspirin was continued until platelet counts normalized and repeated echocardiogram was normal. However, high dose of aspirin was tailored for patients who were persistently febrile and symptomatic.

Recovery was defined by the absence of fever and normalization of inflammatory markers, while relapse was defined as the initial response for a few days and then recurrence of the hyper inflammation state.

Statistical analyses were performed using the Excel statistical package and SPSS 22.0.

Ethical approval

Ethical approval for the study was obtained from the Institutional Review Board (IRB) at the Medical Research Center (MRC), Hamad Medical Corporation, Doha, Qatar (MRC-01-20-142).

Results

Fifteen patients were included in the study (8 females and 7 males) with a mean age of 3.5. \pm 2.7 years. Twelve patients tested positive for SARS-CoV-2 PCR at the time of MIS-C diagnosis while 6 patients had an evidence of recent SARS-CoV-2 infection through serology testing (IgG/IgM) (Table 2). All 15 patients had GI involvement, and 60% of them

had elevated liver enzymes. Two patients had hepatosplenomegaly and one had pan-colitis. Respiratory involvement was reported in 9 patients, 8 of them had radiological evidence of chest infiltrates. Three of the 8 experienced lung collapse and atelectasis, and 4 had evident pleural effusion. Two patients required respiratory support in the form of oxygen by nasal cannula. Four out of the 15 patients had renal involvement. Two (50%) had renal pyelectasis, and one had elevated BUN upon admission, which improved upon re-hydration (25%).

Two patients among the three patients who underwent cerebrospinal fluid (CSF) testing had CSF pleocytosis. None of the three CSF samples were checked for the presence of SARS-CoV-2. However, all other CSF bacterial and viral cultures were negative. There was no significant musculoskeletal involvement among the patients.

The median interval between being exposed to SARS-CoV-2 infection, until the presentation with MIS-C was 22.7 days (interquartile range; IQR). One patient had had asymptomatic infection with SARS-CoV-2 PCR positivity as part of screening of her family, and upon presentation with MIS-C she was still SARS-CoV-2 PCR positive after 5 weeks from the initial PCR testing. Another patient who had initially a negative nasopharyngeal swab for SARS-CoV-2 PCR and negative serology at the time

Table 2. Main clinical characteristics of our patients.

Age in years	3.5 \pm 2.7
Sex: male	7 (46.6%)
With co-morbidities	4 (26.6%)
Ethnicity	
<i>Arabic descent</i>	11 (73.3%)
<i>Asian descent</i>	4 (26.6%)
PICU admission	5 (33.3%)
Mean days of hospitalisation	9.8 \pm 7.3
Mean number of organs involved	4.4 \pm 1.2
Symptoms at presentation	
Fever: equal or > to 3days	15 (100%)
Vomiting	11 (73.3%)
Diarrhoea	6 (40%)
Abdominal pain	5 (33.3%)
Kawasaki-disease features	9 (60%)
Shock-hypotension	2 (13.3%)

Legend: PICU = Pediatric Intensive Care Unit

of MIS-C presentation., had positive SARS-CoV-2 PCR (upon doing nasopharyngeal wash) during his hospital stay.

All patients had fever as a presenting symptom that persisted for three days or longer and a high D-dimer level with a mean of (9.8 ± 10.2 mg/L FEU). 78.5% of patients had high fibrinogen levels. Two patients had a high INR (13.3%); Prothrombin time (PT) and PTT were prolonged in (53.3%) of patients. IL-2 level was elevated in the 3 patients who were checked for IL2 level (3/3). IL-6 level was elevated in 7 out of 9 patients checked for IL6. Triglycerides were elevated in 54.5% of patients (Table 3).

Nine, out of the 15 patients had symptoms and signs of Kawasaki-disease (KD) (60%). Five patients out of them had typical KD features. Two patients presented with Kawasaki shock syndrome and required inotropes support.

Patients with features of KD were relatively younger than patients with non KD.

Echocardiogram abnormalities were only found in patients in KD category (Table 4).

Five patients required PICU admission, and 2/15 required respiratory support. Four of the five had another underlying condition. One patient had asthma, another had a failure to thrive with hypotonia, the 3rd patient had left renal agenesis, and the 4th had chronic thrombocytopenia.

Table 3. Main laboratory data in our patients

Laboratory values (n. and %)	
Leucocytosis	7 (46.6%)
Leukopenia	5 (33.3%)
Lymphocytopenia	11/15 (73.3%)
Neutrophilia	7 (46.6%)
Anaemia	13 (86.6%)
Thrombocytopenia	9 (60%)
Elevated D-dimer (N.V.: <0.44 mg/L FEU)	15 (100%)
Elevated fibrinogen level	11 (78.5%)
Prolonged coagulation profile:	
High PT	8 (53.3%)
High PTT	9 (60%)
High INR	2 (13.3%)
Elevated C-Reactive Protein (CRP)	15 (100%)
Mean level (N.V.: < 5 mg/L)	94.5 \pm 51.1
Elevated erythrocyte sedimentation rate	9/13 (69.2%)
Mean level (N.V.: 0-20 mm/hr)	43.6 \pm 34
Elevated serum ferritin	15 (100%)
Mean level (N.V.: 10-60 ng/L)	607.7 \pm 460
Elevated brain natriuretic peptide	14/14 (100%)
Mean level (N.V.: 0-100 pg/ml)	6.157,5 \pm 8.634
Elevated troponin	8 (53.3%)
Mean level (N.V.: <10 ng/L)	16.2 \pm 32
Elevated procalcitonin	10/12 (83.3%)
Elevated IL-6 level	7/9 (77.7%) (*)
Mean level (N.V.: < 1.8 pg/ml)	102.7 \pm 100
Elevated IL-2 level	3/3 (100%) (**)
Elevated LDH level	5/10 (50%)
Vitamin D deficiency	3/5 (60%)

Legend: N.V.= normal values; (*): In only 9 patients; (**): In only 3 patients.

Table 4. Comparison between our study groups of MIS-C with Kawasaki-disease versus MIS-C with no-Kawasaki-disease presentation

	MIS-C with Kawasaki-Disease (KD)	Non-Kawasaki Disease MIS-C	P value
Number of patients	9	6	-
Gender: male	5 (55.5%)	2 (33.3%)	-
Age (IQR)	3.5 years	5.9 years	-
PICU admission	3 (33.3%)	2 (33.3%)	0.70
Platelets (mean; N.V.:170-450 μL)	173.000	344.000	
Elevated pro-BNP	100% (13.832) IQR	100% (4.025) IQR	0.35
Elevated troponin	44.4%	66.7%	0.60
Echocardiogram abnormalities (Myocardial +Valvular affection + Coronary arteries abnormalities)	3 (33.3%)	0%	0.22

Legend: IQR: Interquartile range; Pro-BNP: pro-B-type natriuretic peptide.

One was refractory to initial treatment and needed Anakinra (IL-1 inhibitor) infusion and required monitoring during the initiation of the therapy. Other PICU admitted patients (4 patients) were in potentially critical conditions and needed to stay in the Pediatric intensive care unit till they are stabilized. One of them was an 8-year-old female with severe pan-colitis, who had deranged coagulation profile, metabolic acidosis and electrolytes imbalance. The other two patients presented with hypotension and a diagnosis of KD-MIS-C, (KD-shock syndrome) and required inotropic and respiratory support. The first one was a 6-year-old male who had severe gastrointestinal symptoms, respiratory insufficiency and hypotension, received fluid pushes and required norepinephrine infusion of 0.05mcg/kg/min (for 3days). His echocardiogram showed many abnormalities in form of patent foramen ovale with minor left-to-right shunt, mild tricuspid valve regurgitation, mild mitral and pulmonary valve regurgitation, and trivial aortic valve regurgitation. He had normal coronary arteries and normal contractility. He required oxygen through nasal canula for two days.

The second was a 6-years old patient who presented with hypotension and acute respiratory failure. His first echocardiogram showed low normal left ventricular systolic function ejection fraction (EF) of 51% by Simpson's method and normal coronary arteries.

His hypotension required norepinephrine infusion for 3 days. Ultrasonography revealed accentuation hepatic periportal echogenicity, engorged hepatic veins and IVC, edema of the gallbladder wall with small amount of free fluid in the pelvis. He required respiratory support for 3 days.

All patients received antibiotics for the first 24 hours of admission until an infection was excluded. All patients received IVIG treatment at a dose of 2 grams per kilogram body weight via local IVIG administration. A total of 8/15 patients received steroids (53.3%) regardless of their need for a second dose of IVIG. Altogether, 9/15 received prophylactic anticoagulant therapy, and none had a thrombotic event. Twelve patients received aspirin. No mortality was reported among the study participants.

Discussion

Fifteen children who were admitted to Pediatric Units of Hamad Medical Corporation with a diagnosis of MIS-C were studied. Our patients had a younger average age (3.5 ± 2.71 years) compared to other international reports (Table 5) and to a systemic review by Abrams et al. (10) in which the age range of 440 patients was 7.3- 10 years. In addition, the male predominance reported by other studies was not evident in our study (8-12).

Table 5. Comparison between our findings and other reports.

Country of the study	Our study	Iran (Ref. 16)	Italy (Ref.6)	USA (Ref.8)
Number of patients	15	45	10	570
Mean age in years	5 (IQR)	7 (IQR)	3 (IQR)	8 (IQR)
Gender: male (%)	7 (46.6%)	24 (53%)	7 (70%)	316 (55.4%)
ICU admission	5 (33.3%)	NA	NA	364 (63.9%)
Average days of hospitalisation	9 days	8 days	NA	6 days
Median duration of fever in days	5 days	NA	6 days	5 days
Average number of organs involved	4.4 ± 1	NA	NA	4
GI symptoms	15 (100%)	48.3% (mean)	6 (60%)	518 (90.9%)
Kawasaki like-presentation	9 (60%)	31 (69%)	10 (100%) *	28 (4.9%)
Mortality	0	(11%)	NA	10 patients (1.8%)

Legend: NA=not available; GI= gastro-intestinal; *The study was conducted on MIS-C patients with Kawasaki-like presentation only

In this study we had 4 patients who were < 1 year of age with 1 neonate. They didn't have severe symptoms at presentation and none of them developed acute cardiac or respiratory deterioration and none required respiratory or inotropic support. One of them had typical KD-MIS-C and he was the only infant with coronary arteries involvement. Two of them were admitted to ICU for monitoring purposes.

A third of our MIS-C patients required PICU admission. Similarly, Ahmed et al. (12) reported a significant percentage of patients diagnosed with MIS-C requiring PICU admission. Close monitoring, especially during medication infusion, was the most common reason for admission to the PICU; however, two of our patients experienced hypotensive shock and required inotropic support.

Consistent with previously reported studies, fever, gastrointestinal and hematological manifestations were present in all patients, and some had respiratory symptoms (8,13). The main gastrointestinal manifestations included vomiting, diarrhea, and abdominal pain with elevated liver enzymes. One patient with pancolitis required PICU admission.

Lung involvement was observed in nine patients, but none required intensive respiratory support. Two patients presented with hypotension and shock and were primarily admitted to the PICU. The CT chest showed bilateral atelectatic changes with mild pleural effusion. They had mild respiratory symptoms and required respiratory support in the form of oxygen by the nasal cannula only. Clinically and radiologically the two patients showed bilateral basilar atelectasis that explained their symptoms. In contrast to our findings, Dufort et al. (14) reported that 10% of their patients required mechanical ventilation, and Riphagen et al. (15) reported that 100% of their patients required respiratory support. Twenty per cent of our patients had an abnormal echocardiogram, and only one patient had coronary dilatation and aneurysm. Whittaker et al. (13), reported that 14% of their patients had coronary dilatation and aneurysm, and other investigators reported a significantly higher percentage of echocardiographic abnormalities (12).

Sixty percent of our patients had KD features with positive serology/PCR for SAR-CoV-2 and fulfilled the criteria for MIS-C. Mamishi et al. (16), reported a similarly fraction of Kawasaki-like features among the MIS-C patients. Our patients with Kawasaki-resembling symptoms presented between June and July 2020, which was slightly later than those reported in European countries (from April to May) (8, 13, 14, 17). In addition, our patients had a higher prevalence of lymphocytopenia, and thrombocytopenia compared to that reported in other studies (8).

Similar to the treatment strategy reported by Dufort et al. (14), all our patients received IVIG, and 53.3% received both systemic glucocorticoids and IVIG. Two of our patients received Anakinra (IL-1 inhibitor) (Table 6); the first patient was a neonate with a relapse resistance to IVIG and pulse steroid MIS-C, and the second infant (1 year old) suffered from cardiac involvement in the form of coronary dilatation and aneurysm. None of our patients received IL-6.

The mean duration of hospitalization was 9.8 days, which was necessary to ensure complete resolution of inflammation. However, one patient had a relapse, and two patients required transfer to a tertiary care pediatric ward for continued hospitalizations. All other patients completely recovered and discharged.

Table 6. Summary of medications used in our MIS-C cases.

Medications received	Dose
Intravenous immunoglobulin (IVIG)	2 g/kg/dose 1 to 2 doses
Methylprednisolone	30 mg/kg/day (As pulse steroids for 3 days)
Prednisolone	2 mg/kg/day
Esomeprazole	1 mg/kg/day
Anakinra	2 mg/kg bolus, then continuous infusion of [(0.02 ml/kg/h)
Aspirin	80 mg/kg/day for 48-72 hours, then 3-5 mg/kg per day
Enoxaparin prophylaxis	1 mg/kg/dose subcutaneous once per day

Their follow up, by a general pediatrician and cardiologist, showed no relapse for 6 months after discharge.

Limitations of this study included a relatively small number of cases; larger groups collected over an extended period in the future are needed for more conclusive findings.

In summary, young patients enrolled in this study who presented with MIS-C had significant manifestations of Kawasaki-like illness compared to patients described in other reports. One infant (1/12) developed a coronary artery aneurysm. MIS-C in infants and children with COVID-19 can lead to a combination of distributive and cardiogenic shock, probably secondary to a hyperinflammatory state. The prognosis in our patients was good. The relation between SARS-CoV-2 and MIS-C in children continue to be elucidated by further research.

Ethics approval: Ethical approval for the study was obtained from the institutional review board (IRB) at the Medical Research Center (MRC), Hamad Medical Corporation, Doha, Qatar (MRC-01-20-142).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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