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ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in Children (MIS-C) Related to SARS-CoV-2 and 1-Year Follow-up

Rashmi Kapoor[1] · Tarun Chandra[1] · Chandra Prakash Singh[1] · Ruchira Singh[1] · Ishita Pandey[1]

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Abstract

Objective To study the demographics, clinical profile, management, outcome and 1-y follow-up of children with multisystem inflammatory syndrome in children (MIS-C).

Methods This was a retrospective observational study of 54 Children satisfying the WHO MIS-C criteria admitted during the study period.

Results Fifty-four children were included in the study, median age was 5.5 (IQR 8.75), 68.5% were males. PICU admissions were 77%. Most involved organ was gastrointestinal (92%), followed by cardiovascular 85%, central nervous system (CNS) 74%, respiratory 72%, mucocutaneous 59%, and renal 31%, and hypotension was the presenting symptom in 43%. Coronary artery dilatation was seen in 1 (1.8%) child. All patients presented with more than three organs involvement. Raised procalcitonin was seen in 100%, raised BNP in 31.5%, low ejection fraction in 83.3%, and abnormal radiograph in 59%. All children were positive for anti-SARS-CoV-2 antibodies and negative for cultures. Methylprednisolone or intravenous immunoglobulin (IVIg) was used in 77%, mechanical ventilation in 18.5%, and inotropic support in 77%. Aspirin was used in 48% and low molecular weight heparin (LMWH) in 54%. The median stay in hospital was 7 d (IQR 2). There was 1 mortality (1.8%). On 7-d follow-up, 98% children had a normal echocardiography; on 6 mo and 1-y follow-up, all children had normal echocardiography.

Conclusion MIS-C is an important complication of COVID-19 infection. Cardiac involvement resolves completely. Coronary artery involvement is not common.

Keywords COVID-19 · IVIg · Kawasaki disease · MIS-C · Methylprednisolone

Introduction

When COVID-19 was first recognized, it was believed that it was almost benign and of little consequence in the pediatric population. Globally, the initial reports indicated that children have lower rates of hospitalization and death than adults [1]. Subsequently, since the emergence of multisystem inflammatory syndrome in children (MIS-C), COVID-19 infections can have serious consequences in children as well [2]. In April 2020, during the peak of the COVID-19 pandemic in Europe, a cluster of children with hyperinflammatory shock was reported in England [3]. Soon after, several European countries, United States, Asia, and Latin America reported the occurrence of such hyperinflammatory process in children, possibly related to SARS-CoV-2 infection [3–7]. The patients' signs and symptoms were temporally associated with COVID-19 but presumed to have developed 2–4 wk after acute COVID-19 [8]. MIS-C is characterized by fever, elevated inflammatory markers, and high levels of both pro- and anti-inflammatory cytokines. According to the available literature till now, the spectrum of MIS-C is a combination of typical/atypical Kawasaki disease (KD), toxic shock syndrome (TSS), and macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH) with prominent involvement of mucocutaneous, gastrointestinal, cardiovascular, or neurological systems [9]. The prevailing hypotheses for the pathogenesis of MIS-C are: 1) a postinfectious autoimmune-mediated inflammatory process, 2) a cytokine storm instigated by a superantigen

✉ Rashmi Kapoor
rashmiregency@gmail.com

[1] Department of Pediatrics, Regency Hospital, A-2, Sarvodaya Nagar, Kanpur, Uttar Pradesh 208005, India

Table 1 Children fulfilling the WHO criteria for MIS-C ($N = 54$)

	WHO criteria for MIS-C [11]	(*N*) %
	Children with fever	(54)
	And	100%
A	**Any two of the following**:	
A1	Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet)	(31) 59.3%
A2	Hypotension or shock	(23) 42.6%
A3	Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP).	(46) 85%
A4	Evidence of coagulopathy (by PT, PTT, elevated D-dimers)	(15) 28%
A5	Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)	(50) 92.6%
	And	
B1	Elevated markers of inflammation such as elevated C-reactive protein	(43) 79.6%
	Or	
B2	Elevated markers of inflammation such as elevated procalcitonin	(54) 100%
	And	
C	No other obvious microbial cause of inflammation including bacterial sepsis, staphylococcal or streptococcal shock syndromes	None
	And	
D	Evidence of COVID-19 (serology)	(54) 100%

response, and 3) a dysregulated immune response to chronic exposure to SARS-CoV-2 viral antigens [10].

Material and Methods

The two MIS-C peaks had a temporal relation with two COVID-19 waves in India (1st wave from August to October in 2020 and the 2nd sharp wave in April/May in 2021). The data of 54 children from 30th September 2020 to June 6th 2021, conforming to the case definition of MIS-C by WHO [11] were collected. Patients with hemodynamic instability (requiring ionotropic support or fluid resuscitation), and or organ failure were admitted to pediatric intensive care unit (PICU) and were categorized as severe MIS-C, and all those hemodynamically stable, but needing hospitalization were categorized as moderate MIS-C. Bedside echocardiography and cardiac triaging is done for every critically ill child coming to the authors' emergency department, suspected to be having sepsis. If MIS-C or any cardiac abnormality is suspected, patients are subsequently seen by a pediatric cardiologist. Cases of tropical fevers like dengue, scrub typhus, leptospirosis, malaria, enteric, and viral exanthems are endemic during the monsoon season, and therefore, the authors screened for these diseases. A positive dengue IgM ELISA/RT-PCR, scrub typhus card test, leptospira IgM, malaria card test/peripheral smear, blood culture for salmonella, were taken as diagnostic for specific tropical disease and were excluded from the study. Patients with a positive blood or urine culture, negative SARS-CoV-2 antibodies, and newborns were excluded from the study.

The data were collected on the following parameters: demographics, clinical findings, echocardiography, radiology, laboratory investigations, treatment received including intensive care interventions and outcome. After discharge 7-d, 6-mo, and 1-y follow-ups in the outpatient department with echocardiography were noted in the datasheet. For statistics, MS Excel was used for descriptive analysis: count, mean/median, standard deviation (SD)/(IQR). Continuous variables were expressed as mean and SD, medians and interquartile ranges, and categorical variables were expressed as counts and percentages.

Results

The present study included 54 children; median age was 5.5 y (IQR 8.75), 68.5% were males. Children less than 5 y were 50%. PICU admissions were 77%. Most involved organ was gastrointestinal (92%), followed by cardiovascular 85% (marked by reduced ejection fraction, abnormal echocardiography, or raised cardiac enzymes). CNS involvement in the form of headache, irritability and seizures was present in 74%, 1 presented as acute encephalitis syndrome and 1 as Guillain–Barré syndrome (Table 1). Hypotension was the presenting symptom in 43% children. Coronary artery dilatation was seen in 1 (1.8%) child. All patients presented with more than three organ involvement. Raised procalcitonin was seen in 100%, raised BNP in 31.5%, 74% children came with thrombocytopenia, low ejection fraction in 83.3%, and abnormal radiograph in 59%. All children were positive for anti-SARS-CoV-2 antibodies (Table 2). Methylprednisolone or IVIg was used in 77%; only methylprednisolone was given in 18%; both methylprednisolone and IVIg were given in 58% of children; a repeat dose of IVIg was given to 5.6%. Mechanical ventilation was needed in 18.5%, whereas noninvasive ventilation was given in 27.8%. Inotropic support was given in 77%. Aspirin was used in 48% and LMWH in 54% (Table 3). Median stay in hospital was 7 d (IQR 2). There was 1 mortality (1.8%). On 7-d follow-up after discharge, 98% children had a normal echocardiography and inflammatory markers, except for one who had a coronary artery dilatation > 2 z score; on 6-mo and 1-y follow-ups, all children had complete cardiac recovery.

Table 2 Abnormal laboratory parameters and other investigations

Parameters	%	Median (IQR), Mean (SD)
Raised procalcitonin (> 0.02 ng/mL)	100	Median 3.7 (31.1)
Raised CRP (> 0.5 mg/dL)	79.6	Median 12.0 (26.9)
Raised troponin I (> 0.02 ng/mL)	37.0	Median 0.07 (0.16)
Raised BNP (> 100 pg/mL)	31.5	Median 220.0 (831)
Raised CKMB (> 4.3 ng/mL)	51.9	Median 12.0 (29.6)
Neutrophilia	20.4	Mean 73.4 (15.4)
Lymphopenia	13.0	Mean 19.4 (8.4)
Thrombocytopenia < 150000	74.1	
INR > 1.49	27.8	Median 1.6 (0.24)
Raised SGOT	61	
Raised SGPT	48	
EF < 54%	83.3	Median 50.0 (15.0)
Abnormal echo (low EF, MR, dilated RA, dilated RV, TR)	46.3	
Dilated coronaries	1.8	
Abnormal radiograph (b/l patchy opacity in chest radiograph, ground glass opacity in chest radiograph, or mild pleural effusion)	59.3	
Raised anti-SARS-CoV-2 spike protein antibody IgG > 0.8 U/mL	100	Median 75.2 (118.0)

BNP Brain natriuretic peptide, *CKMB* Creatinine kinase myocardial band, *CRP* C-reactive protein, *EF* Ejection fraction, *IgG* Immunoglobulin G, *INR* International normalized ratio, *MR* Mitral regurgitation, *RA* Right atrium, *RV* Right ventricle, *SARS-CoV-2* Severe acute respiratory syndrome coronavirus 2, *SGOT* Serum glutamic oxaloacetic transaminase, *SGPT* Serum glutamic pyruvic transaminase, *TR* Tricuspid regurgitation

Table 3 Treatment modalities

Modality	*n* (%)
Immunomodulators used	42 (77%)
Only methylprednisolone	10 (18%)
Only IVIg	1 (1.8%)
Both IVIg + methylprednisolone (combination)	31 (57.4%)
Repeat dose of IVIg & escalation of methylprednisolone	3 (5.6%)
Mechanical ventilation	10 (18.5%)
Noninvasive ventilation	15 (27.8%)
Inotropic support	42 (77%)
Aspirin	25 (48.1%)
LMWH	28 (53.7%)

IVIg Intravenous immunoglobulin, *LMWH* Low molecular weight heparin

Discussion

Feldstein et al. [12] studied a cohort of 539 MIS-C patients throughout the United States and demonstrated a nearly 75% ICU admission rate, 45% vasopressor requirement with less than 2% mortality, with the majority of patients achieving a complete recovery. In the present study, 77% were PICU admissions, 77% with inotropic support, and 1.8% mortality. In the present study, the median age was 5.5 y, IQR (8.75), which is lower than in other published reports [13, 14]. Majority of studies [2–4, 8] have reported gastrointestinal involvement as the commonest followed by cardiovascular, which is similar to the authors' observation. The present study has reported 42% children with hypotension and shock, 85% children had cardiac involvement in the form of raised cardiac enzymes or low ejection fraction, which was observed in most studies [15, 16]. Different studies found abnormal radiographs in around 30%–35% of cases [2, 5, 15, 16]. Abnormal radiographs were found in 59% of the present cases. It was observed that 23% children in the present study admitted to the wards, did not receive any immunomodulators, and there was no difference in the

outcome. Davies et al. [17] found no evidence of a difference in response in clinical markers of inflammation between patients with MIS-C, who were treated with IV immunoglobulin, steroids, or biologics, compared with those who were not. McArdle et al. [18] found no evidence that recovery from MIS-C differed after primary treatment with IVIg alone, IVIg plus glucocorticoids, or glucocorticoids alone. One study [19] found that among children and adolescents with MIS-C, initial treatment with IVIg plus glucocorticoids was associated with a lower risk of new or persistent cardiovascular dysfunction than IVIg alone. Sugunan et al. [20] reported that methylprednisolone pulse therapy was associated with favorable short-term outcomes. In the present study, methylprednisolone or IVIg was used in 77%; no biologics were used in any of the present patients. Treatment of MIS-C following COVID-19 has been instituted on the basis of experience with treatment of KD. No randomized clinical trial of long-term effects of IVIg in KD has been performed since 1990. The use of steroids has more evidence than IVIg, none of the studies show a clear evidence for use of salicylates. More studies and robust clinical trials are needed to determine the most effective and efficient therapies to treat serious and life-threatening complications of MIS-C [17].

The study has a few limitations. As the data were collected from the paper and electronic medical records, some data might have been missed. Some cases might also have been missed because the understanding of the clinicians about MIS-C was not uniform, and the tests needed to confirm the case definition might not have been ordered.

Conclusion

MIS-C is an emerging new syndrome, and the understanding about it is evolving. The cardiac complications that are common at the time of presentation resolve completely in most cases. Even though the younger children are asymptomatic for acute SARS-CoV-2 infection, they are at a risk for this serious post-COVID complications.

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Authors' Contributions RK: Concept, design, preparation and finalizing the draft, review literature, critical revision; TC: Preparing the draft, collating the data, review literature; CPS: Collecting data and treatment of patients; RS, IP: Data collection and entry, care of the patients. RK will act as the guarantor for this paper.

Declarations

Ethics Approval Clearance from the hospital internal ethics committee has been taken. The approval no is RHL-IEC-16078.

Conflict of Interest None.

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