

Original Research Article

Multisystem inflammatory syndrome in children in Coastal Andhra, India

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ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) associated with COVID is a recently emerged disease and there is limited Indian data. We reported the presentation and clinical course of these children.

Methods: All children who had symptoms and signs of MIS-C according to WHO criteria and those positive for SARS-CoV-2, were considered for the study. Clinical features, lab parameters, treatment details and outcome were documented.

Results: 104 children, who had MIS-C during the study period. Out of them, 52 (50%) required respiratory support. Among those who required respiratory support 13 (12%) children required invasive ventilation, 11 (10.5%) children could be managed with noninvasive ventilation, whereas 28 (27%) children required supplemental oxygen. 18 (17%) children had signs of myocarditis and left ventricular dysfunction. 12 (11.5%) children had pulmonary edema and Coronary artery dilatation was present in 4(4%) cases. Steroids were used as main stay of therapy. Low dose intravenous methylprednisolone was administered to 72(69%); pulse dose methylprednisolone was administered to 12 (12%) children. Intravenous immunoglobulins (IVIG) administered to 20 (19%) children. Among the study group, 103 children survived and one child expired (0.96%).

Conclusions: Optimal use of immunomodulators and frequent hemodynamic assessment with functional ECHO to optimize the inotropes, can improve the outcomes among those with myocardial dysfunction.

Keywords: MIS-C, Multisystem inflammatory syndrome, COVID, Pediatric

INTRODUCTION

Initially reports suggested that children were disproportionately spared from SARS-CoV-2 infection, even if they are infected, they were highly resistant and had mild symptoms.^{1,2}

Since April 2020 to May 2020 many countries started to report a new hyperinflammatory disease that was associated with SARS-CoV-2 infection. MIS-C was initially reported in UK and Italy, subsequently from

New York and other parts of the U.S.^{3,4} The Royal College of Paediatrics and Child Health (RCPCH) labelled this clinical syndrome as pediatric MIS temporally associated with COVID-19 (PIMS-TS).⁵ Subsequently with increased incidence globally, this illness was labelled multisystem inflammatory syndrome in children (MIS-C) by the CDC and the WHO.^{6,7} The definition across by different bodies is based on these elements: age, persistent fever, presence of laboratory markers of inflammation, manifestation of signs or symptoms of organ dysfunction, lacking an alternative

diagnosis and a temporal relation to SARS-CoV-2 infection or exposure. There is paucity of data from India on MIS-C, especially regarding the differences in disease severity after the first wave and second wave, hence we conducted this study to describe clinical features and management in children with MIS-C.

METHODS

This was the analysis of the observational study from the division of paediatric intensive care from division of Pediatric Intensive care in Medicover Women and Child Hospital and Maharajah Institute of Medical Sciences. This study was conducted from August 2020 to September 2021, following first wave and second wave of COVID-19 infection. Children with MIS-C who fulfilled the WHO criteria were included in the study.⁷ Institute Ethical Committee approval was obtained. All children who had symptoms and signs of MIS-C according to WHO criteria and those positive for SARS-CoV-2 exposure (who were tested positive by the nasopharyngeal swab RT-PCR technique/rapid Ag/positive for IgG and IgM antibodies; contact positive) were considered for the study. Other causes with similar clinical presentation like dengue shock syndrome, bacterial sepsis and toxic shock syndrome were excluded prior to diagnosing the child with MIS-C. Demographic variables were recorded and COVID status was investigated. Clinical features, lab parameters, treatment details and outcome were documented.

Following evaluation were done in all cases. Baseline laboratory parameters like Complete hemogram and c-reactive protein, liver function, renal function, blood gases analysis, blood cultures were evaluated at time of admission and repeated as required. Specific laboratory markers serum ferritin, D-dimers, and cardiac biomarker-troponin I was done. COVID infection was diagnosed by nasopharyngeal swab RT-PCR and/or COVID antibody test as recommended by Indian Council for Medical Research (ICMR). Functional echocardiography was done in 1st hour of admission and 2nd ECHO done by Pediatric cardiologist in first 12 hour of admission. Ventricular dimensions, myocardial dysfunction and coronary ectasia or aneurysm were assessed. All cases were under continuous cardiac monitoring. Serial functional ECHOs were done to titrate fluid resuscitation and Inotropes. Cardiac rhythm abnormalities and myocardial ischemia was assessed on electrocardiogram. Shock was labelled if child had hypotension with poor peripheral perfusion after fluid resuscitation >20 ml/kg and required inotropic support. Myocarditis was defined as cardiac dysfunction with LV ejection fraction <50% on echocardiography and elevated cardiac biomarkers. Patients who presented with shock and LV dysfunction were classified primarily as cardiogenic shock. The coronary artery diameters were measured as per standard criteria and indexed with Z scores.^{8,9} Coronary Z scores of greater than 2.5 were considered as dilated.⁸

Statistical analysis

SPSS (IBM, USA) was used for performing the statistical analysis. Chi-square test was used to compare categorical variables, student t test was used to compare normally distributed data and Mann Whitney U test was used to compare data which was not normally distributed.

RESULTS

A total of 104 children with MISC were treated during the study period. Out of them, 55 (53%) were males. Mean age at presentation was 6.7±3.5 yrs. Demographic variables and SARS-CoV-2 status are presented in Table 1. There were 27 (26%) children below 5 years of age. Duration of stay ranged from 3-14 days with mean of 7 days. 69 (67%) children were admitted to pediatric intensive care unit.

Table 1: Demographic and clinical parameters in the study group.

Demographic parameters	Total cases (n=104)
Age (years)	6.7±3.5
Males (N, %)	55 (53)
Fever duration (m ±SD) (days)	4.8±1.8
Rash (N, %)	34 (33)
Pain abdomen (N, %)	46 (45)
Diarrhea/vomiting (N, %)	32 (31)
SARS-CoV-2 status	
RT-PCR positive (N, %)	17 (16.6)
Antibody positive (N, %)	87 (84.3)
H/o contact (N, %)	16 (15.6)

Among the hematological parameters, 50 (48%) children had thrombocytopenia. Biochemical and echocardiographic parameters are presented in Table 2. C-Reactive Protein was elevated in all the cases and ranged between 10-470 mg/dl. Serum Ferritin levels were >2000 ng/ml for 32 (31%) children and 1000-2000 ng/ml for 12 (12%) children. D-dimers ranged from 450-9200 ng/ml with a mean of 4075 ng/ml. Serum troponin I levels ranged from 8-520 ng/ml with a mean of 14.5 ng/m.; Troponin was elevated in 27 (26%) children. Blood cultures obtained at admission were negative in all cases.

Out of 104 children, 52 (50%) required respiratory support. Among them 13 (12%) children required invasive ventilation, 11 (10.5%) children could be managed with noninvasive ventilation, whereas 28 (27%) children required supplemental oxygen. 18 (17.3%) children had signs of myocarditis (LV dysfunction). 12 (11.5%) children had pulmonary edema and Coronary artery dilatation was present in 4 (4%) cases.

During the PICU stay, 23 (22%) children required either platelets transfusion or fresh frozen plasma. 29(28%) children had shock at admission. The details of inotropes

that were used as follows: Milrinone alone in 13 (12%), Noradrenaline alone 4 (4%), Milrinone in combination with Noradrenaline in 8(8%) Dobutamine alone in 4(4%) children. Steroids were used as main stay of therapy. Pulse dose intravenous methylprednisolone was administered to 12 (12%) children; Low dose Methylprednisolone was administered to 72 (69%); Intravenous immunoglobulins (IVIG) administered to 20 (19%) children. 36 (35%) children were given Ecosprin. LMW heparin was required by 10 (10%) children. 103 children survived and 1 (0.96%) child expired. The expired child had preexisting co-morbidity i.e., cerebral palsy. We have compared the hematological parameters between ‘those with Shock’ Vs. ‘those without Shock’ (Table 3). Serum Ferritin levels and Troponin levels were significantly more in those with shock at admission.

We have done subgroup analysis, diving the study period in to 2 epochs, i.e., 1st wave of COVID (August 2020 to February 2021) and 2nd wave of COVID (March 2021 to September 2021). The data is presented in Table 4.

The proportion of children who had respiratory distress in first wave was more than second wave [27 (64%) Vs. 25 (40%), p=0.02]. The proportion of children who had

myocardial dysfunction in first wave was more than second wave [11 (26%) Vs. 7 (11%), p=0.04]. The proportion of children who required blood products in first wave was more than second wave [13 (31%) Vs. 10 (16%), p=0.04]. The proportion of children who had Shock at admission in first wave was more than second wave [19 (45%) Vs. 10 (16%), p=0.004].

Table 2: Biochemical and echocardiographic parameters.

Baseline hematological parameter	Total cases n=104 Mean (SD)
Total leucocyte count cells/cumm	14,200± 8200
Neutrophils (%)	78±10
Lymphocytes (%)	13±8
Hemoglobin (g/dl)	9.5±2.1
Platelets (lakh/cumm)	1.6±1
SGPT (IU/L)	92 (20, 160)
CRP (IQR)	162 (16, 281)
Ferritin (mcg/l)	653 (262,1550)
D-dimer (ng/ml)	4075 (651, 7380)
Troponin-I (ng/ml)	14.5 (6, 195)

Table 3: Comparison of haematological parameters in Shock Vs No Shock group.

Specific hematological parameter	Shock n=38 (36%)	No shock n=66 (64%)	P value
Sr. ferritin(ng/dl) median (IQR)	920 (410, 1900)	335 (82, 410)	0.01
D-Dimers (ng/dl)	5700 (1800, 12600)	3200 (720, 8200)	0.2
Sr. Troponin I (ng/dl)	82.6 (11, 350)	6 (0.2, 10)	0.001
Deranged LFT	20 (53%)	7 (11%)	0.03

Table 4: Comparison of data in first wave (Epoch 1) Vs Second wave (Epoch 2).

	Total (N=104)	Epoch 1 (N=42) (Following 1 st wave)	Epoch 2 (N=62) (Following 2 nd wave)	P value
Respiratory distress (%)	52 (50%)	27 (64%)	25 (40%)	0.02
Invasive ventilation (%)	13 (12%)	8 (19%)	4 (9.5%)	0.06
Non-invasive ventilation (%)	11 (10.5%)	4 (10%)	8 (13%)	0.7
Oxygen administration	28 (27%)	15 (36%)	13 (21%)	0.12
Left ventricular dysfunction	18 (17.3%)	11(26%)	7 (11%)	0.04
Pulmonary edema	12 (11.5%)	7 (17%)	5 (18%)	0.2
Coronary dilatation	4 (4%)	2 (4.7%)	2 (3%)	1
Blood product requirement	23 (22%)	13 (31%)	10 (16%)	0.04
Shock	29 (28%)	19 (45%)	10 (16%)	0.004

DISCUSSION

COVID-19 pandemic has spread throughout the world at an alarming rate.¹⁰ Initial reports suggested that children who got infected are highly resilient to the disease and generally progress with a mild course.^{1,11} Awareness has increased regarding MIS-C among the paediatricians and health care professionals after second wave as compared to first wave. Literature suggests MIS-C affects only 0.6% of patients <21 years of age infected with SARS Cov-2 and there are certain limitations in its recognition

and diagnosis.^{12,13} Another major concern was that despite an asymptomatic or milder course of COVID disease children could still develop MIS-C.¹⁴ The literature reports that MIS-C typically manifests 3-4 weeks after SARS-CoV-2 infection.¹⁵ This may explain why many children had positive antibodies to SARS-CoV-2, but negative RT-PCR at the time of MIS-C evaluation.¹⁶ In our study RT-PCR is also positive in 17% of cases. As described by Riphagen et al hyperinflammatory shock is a common element in MIS-C.³ These findings were substantiated in the systematic review by Ahmed et al, which included 662 children.¹⁷

Now the testing guidelines for COVID-19 RT-PCR and other inflammatory markers have now been streamlined in most parts of India. As there is clinically significant overlap with other common diagnoses, there is high probability that clinicians are either missing the milder cases or even over-diagnosing similar presentations of KD or toxic shock syndrome as MIS-C.¹³ Whitaker et al have proposed three clinical patterns of MIS-C presentation *viz.*, those with shock and cardiac involvement, those with fever and elevated inflammatory markers without features of KD, and those who had classical features of KD.¹⁸ An overlap of several children can occur having mucocutaneous features of KD, raised inflammatory markers and those who present with shock.

The inflammatory storm observed in MIS-C is much more intense than KD and TSS, though they few common features. Some differentiating clinical characteristics found in MIS-C includes age of presentation, GI disturbances like vomiting, diarrhoea, and abdominal pain. One more important difference to identify between KD and MIS-C is that approximately 5% of children with Kawasaki's disease presented with cardiovascular collapse, where as 60.2% of children with MIS-C presented with shock.^{17,19}

The reason why few children are more susceptible to develop MIS-C is still unknown. In the systematic review it was observed that the African American/Afro-Caribbean population had more proportion of MIS-C. MIS-C can even present as an acute surgical abdomen. The abdominal pain in MIS-C can be so severe that some were presumed to have appendicitis or surgical abdomen. In studies by Belhadjer et al and Dasgupta children received urgent abdominal surgery, but ultimately found the patients had mesenteric lymphadenitis.^{20,21} As per the definition of MIS-C, neutrophilia and lymphocytopenia were frequent. The average neutrophils percentage was 80.7%, a finding that was reported in 99 children from New York by Dufort et al (average=82.3%).¹² We had similar kind of Neutrophilia in our study. Out lymphocyte percentage also aligned with that of study by Dufort et al as expected, inflammatory markers were universally elevated, additionally elevated serum ferritin, troponin and liver enzymes were significant laboratory parameters observed in patients with shock. Another study from India by Jain et al had similar findings.²² Dufort et al reported KD/KD like illness in 36%, myocarditis in 53%, shock in 10% and coronary aneurysms in 9% of their cohort of children with MIS-C from New York.¹² In a study from Chennai, India, Dhanalakshmi et al reported hypotension requiring vasoactive medications in 57% of patients presenting with PIMS-TS and coronary artery changes in 16%.²³

In classifying patients with MIS-C with KD like illness, clinicians need to differentiate this from classical KD in patients from COVID-19 endemic areas.²⁴ There was significant epidemiological evidence that MIS-C was distinct from KD. When compared with those of classical

KD children with MIS-C were older and sicker. Feldstein et al had observed 50% MIS-C patients presenting with cardiovascular shock leading to vasopressor or inotropic support as compared to only 5% of children with KD in the United States.²⁵ Similarly, in our series, the mean age of patients was 6.7 years, which is older than the age of presentation for KD. The cardiac biomarkers (NT pro BNP, troponin and CPK-MB) were of course indicative of myocarditis and can be used to predict clinical deterioration and shock.

Cardiac manifestations were frequently found in children with MIS-C. Some children developed poor ejection fraction or dilated coronaries in the later part of illness in spite of normal echocardiogram during admission. The most common echo finding was decreased ejection fraction (45%) in systematic review. In line with these findings, a recent study revealed that adults who recently recovered from COVID-19 had ongoing cardiac involvement and myocardial inflammation.²⁶ Accordingly, children undergoing evaluation for MIS-C should have a baseline 2D ECHO, ECG and repeat imaging to follow cardiac function and artery changes. Close follow up will be important as the long-term implications of MIS-C cardiac involvement are currently unknown. Elevated troponin levels in individuals with COVID-19 are independent prognostic markers of poor outcome.²⁷ This implied that all patients with MIS-C would need serial echocardiographic surveillance for coronary and myocardial involvement in the acute and convalescent phase of illness, even if the initial echocardiogram was normal.

Our findings in first wave are comparable to those published in systematic review in which 61% of children required vasopressor support and/or fluid resuscitation.¹⁷ In our series, following first wave 45% required inotropic support, but in the cumulative data, 28% required inotropic support. In the US MIS-C series, IVIG (77%) and systemic glucocorticoids (49%) were used in most patients.²⁵ In the UK series, 71% received IVIG and 64% corticosteroids. Three patients received anakinra and eight received infliximab. Inotropic support was required in 47%.¹⁸ In our series, 69% of the patients received low dose methyl prednisolone and 12% pulse dose; and 19% IVIG. Biologicals such as tocilizumab/infliximab were not used. The relatively lower usage of IVIG is due to high cost of this treatment, which unfortunately is often a deciding factor for treatment decisions in our population.

Based on our small numbers, we do not believe that at present, levels of acute phase reactants can reliably predict the subsequent clinical course of the child. Generally, the short-term outcomes of MIS-C have been promising. The mortality was 1.8% in systematic review.¹⁷ In our series one child expired (0.96%), who has pre-existing cerebral palsy. Although significant proportion of children were critically ill and had multisystem inflammation, all responded to prompt

administration of anti-inflammatory agents, i.e. steroids and IVIG.

The children who presented after first wave had higher incidence of respiratory distress at admission, myocardial dysfunction, shock at admission and blood product requirement. The possible mechanisms need to be further investigated. However, the differences could be attributed to late referrals from peripheral hospitals in first wave because of lack of awareness at that time and also due to lack of access for transport because of strictly imposed lockdown. After first wave national wide treatment protocols and guidelines were established, which helped many paediatricians to initiate the treatment early. However, we didn't see recurrence in any child in the second wave.

These results were analysis of ongoing hospital based prospective study. We were rigid in our case selection to include only those patients who themselves or whose immediate family contacts had confirmed SARS-CoV-2 antigen or seropositivity. Hence, we may have missed mild cases.

CONCLUSION

Frequent hemodynamic assessment with repeated functional Echo and optimal use of inodilators like milirinone can improve the outcomes among those with myocardial dysfunction. Our data is expected to add to the limited data on this condition from India, and assist clinicians in identifying and managing MIS-C.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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