Section: Paediatrics

Case Series

# MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) ASSOCIATED WITH 2019 NOVEL CORONAVIRUS (SARS-COV-2) INFECTION IN INDIA; A CASE SERIES

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused widespread morbidity and mortality, impacting nearly every nation in the world. Though the majority of infected children appear to be spared from severe illness, an unusual pediatric syndrome called multisystem inflammatory syndrome in children (MIS-C), an uncommon complication of COVID-19 that is characterized by prominent cardiovascular, gastrointestinal, and mucocutaneous signs and symptoms associated with prior SARS-CoV-2 infection and present an additional challenge in this ongoing public health crisis. This case series pertains an observation on five patients, aged 2-13 years, who were admitted to the hospital and found to be COVID-19 positive on testing. All patients had history of contact with COVID-19 positive confirmed family members. Most common symptoms were fever (n=5), Rash, Conjunctivitis (n=5), oral ulcers (n-5), Vomiting and Diarrhea (n=3). No patient had any pre-existing co-morbidity. Raised levels of C - reactive protein (CRP), D-dimer and Serum Ferritin were present in all patients. The mainstay of management was Corticosteroids and IV Immunoglobulins. Supportive therapy along with antibiotics (Azithromycin and Doxycycline) and anticogulants Aspirin was given to all children. Mean duration of hospital stay was 14.6 days. One patient required intensive care support. All patients recovered at discharge.

## INTRODUCTION

MIS-C is a newly defined post-viral myocarditis and inflammatory vasculopathy of children following COVID-19 infection. The coronavirus disease 2019 (COVID-19) pandemic has caused widespread mortality and morbidity. Though children are largely spared from severe illness, a novel childhood hyper inflammatory syndrome presumed to be associated with and subsequent to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has emerged with potentially severe outcomes.[1]

Multisystem inflammatory disorder in children (MIS-C) most commonly affects young, school-aged children and is characterized by persistent fever, systemic hyperinflammation, and multisystem organ dysfunction.[2] Although COVID-19 was relatively mild in most children, multisystem inflammatory syndrome in children (MIS-C) subsequently evolved as a post-infectious inflammatory condition associated with abnormal immune function, left ventricular cardiac dysfunction, coronary artery aneurysms, atrioventricular block and clinical deterioration with multiorgan involvement.[3]

A minority of children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) present with multisystem inflammatory syndrome in children (MIS-C), usually 2 to 4 weeks post-infection, the pathophysiology of which is still unclear. The clinical features of this syndrome overlap with Kawasaki disease (KD), toxic shock syndrome (TSS), and secondary hemophagocytic lymphohistiocytosis/ macrophage activation syndrome; although the clinical picture keeps on evolving.[4]


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Many cases go undiagnosed for lack of COVID -19 like symptoms and unawareness among treating clinicians about this newer clinical entity. Further, antibody testing and inflammatory markers are not easily available in many of the Indian hospitals especially in rural India where the second wave had been intense, thereby making it difficult for the diagnosis of MIS-C. Although severe cases of COVID-19 in children including hypotension and multisystem involvements and fatal cases have been reported, majority of the paediatric cases recover within one to two weeks of disease onset.[5,6] The recording of clinical profile and treatment outcome in pandemic is required. This may help in early recognition, appropriate and effective management of this new disease entity. Therefore, the present case series pertains to clinical profile and outcome of children, who presented at a tertiary-care centre of a teaching hospital.

## CASE SERIES

There were five cases of COVID-19, aged 10-17 years, who were admitted to a tertiary care centre of a teaching hospital during the period of July to November, 2020. There were four male child and one female child. Baseline characteristics of patients at admission are presented in [Table1].

The Centers for Disease Control and Prevention (CDC) has declared MIS-C to be a reportable illness as of 14 May 2020, and has provided a case definition which includes- patients under 21 years of age with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours), laboratory evidence of inflammation [one or more of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin)], severe illness needing hospitalization, and involvement of two or more organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological), with positive testing for SARS-CoV-2 indicating current or recent infection or COVID-19 exposure; and no other alternative plausible diagnoses.[7]

Here in this present case series, all of our patients were compliant with the current case definition as given by CDC. All of them presented with multisystem disease with elevated inflammatory markers. Upon testing to detect SARS-CoV- 2 infection was positive in all patients.

All children had at least one family member infected with COVID-19. Categorisation of COVID-19 disease in to mild, moderate and severe was done as per Ministry of Health and Family welfare, Government of India.[8] The patients were tested for COVID-19 by quantitative real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) method using nasopharyngeal swab.

**Clinical Manifestations:** All children presented with high grade fever with mean duration of 5-7 days. The clinical features are presented predominance of mucocutaneous features with rash, conjunctivitis and oral cavity changes being the most common findings. This was followed by irritable in child (4/5), refusal to feed, gastrointestinal manifestations like abdominal pain, vomiting in 3 cases and diarrhea in one case. Respiratory symptoms like cough and dyspnea was found in only one among our cases. Bleeding manifestation and decreased urine output was reported in one case. Signs of shock were present in one case.

**Laboratory Parameters:** Due to a lack of uniformity in the reporting format, laboratory investigations and treatment profile of individual cases are presented in a tabular format [Table2].

The most common hematological abnormalities reported were lymphopenia and neutrophilia and microcytic hypochromic anaemia. Thrombocytopenia was reported in one case.

The acute inflammatory markers ESR and acute phase reactants were elevated in all 5 patients.

Elevated serum ferritin levels and D-dimer levels were detected in all patients.

In our study Chest Xray did not show any abnormality, echocardiography findings showed coronary dilation in all cases.

**Management:** The treatment approach followed in the included case series has been summarized in [Table 2]

Corticosteroids were the most commonly administered therapy for all cases with dose 2mg/kg body weight for maximum duration for 5 days; followed by intravenous immunoglobulin for 60% of cases. Depending on the finding in Echo all patients were given Aspirin an anti-coagulative dose of 3mg/kg for a duration ranging from 3 weeks to 6months. The antibiotics used were Tab. Azithromycin 10mg/kg body weight for duration of 5 days for 40% cases and Tab. Doxycycline 4mg/kg body weight for 5 days was administered to 80% cases as a supportive management, along with Tab. Ivermectin 0.2 mg/kg was given to three patients, each for five days. Mechanical ventilation was provided to around 2 cases to manage the respiratory insufficiency.

Two patients needed oxygen therapy at the rate of 2 L/ min for 48 hours. One of the cases required Intensive Care Unit (ICU) admission. All children were discharged from the hospital with stable Vitals. Mean duration of hospital stay was 14.6 days (range 11-17 days).

**Table 1: Baseline characteristics and Diagnosis of patients.**

| Parameters | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| Age | 11yrs | 2yrs | 3yrs | 6yrs | 11yrs |


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| | | | | | |
|---|---|---|---|---|---|
| Gender | Male | Female | Male | Male | Male |
| H/o Covid-19 Contact in Family | YES | YES | YES | YES | YES |
| Presenting Symptoms | | | | | |
| High grade fever | + | + | + | + | + |
| Red eyes | + | + | + | + | + |
| Oral ulcer | + | + | + | + | + |
| Diarrhea | - | - | - | - | + |
| Vomiting | + | - | - | + | + |
| Abdominal pain | + | - | - | + | + |
| Rash | + | + | + | + | + |
| Bleeding manifestation | - | - | + | - | - |
| Cough | - | + | - | - | - |
| Dyspnea | - | - | + | - | - |
| Refusal of feed | + | + | + | - | - |
| Decreased urine output | - | - | + | - | - |
| SIGNS | | | | | |
| Irritable and lethargy | + | + | + | + | + |
| Bulbar Conjunctivitis | + | + | + | + | + |
| Hypotension | - | - | + | - | - |
| Shock | - | - | + | - | - |
| Tachycardia | - | - | + | - | - |
| Diagnosis | Misc with inflammatory syndrome | Misc with kawasaki phenotype | Misc with shock | Misc with inflammatory syndrome | Misc with inflammatory syndrome |

**Table 2: Investigations and outcome of COVID-19 patients.**

| **Parameters** | **Case 1** | **Case 2** | **Case 3** | **Case 4** | **Case 5** |
|---|---|---|---|---|---|
| CBC | 10.9 | 9.8 | 6.8 | 10.4 | 7.2 |
| Haemoglobin (g/dl) | 10.8 | 7.7 | 10.4 | 9.8 | 11.2 |
| ESR | 62 | 72 | 75 | 68 | 66 |
| Platelet | 2.5 Lakhs | 10.1 Lakhs | 1.4 Lakhs | 2.3 Lakhs | 1.9 Lakhs |
| Acute phase Reactants CRP | Elevated | Elevated | Elevated | Elevated | Elevated |
| Prothrombin Ratio | Normal | Normal | Normal | Normal | Normal |
| PT-INR | Normal | Normal | Normal | Normal | Normal |
| Serum ferritin (ng/mL) (12-140) | 1980 Elevated | 1789 Elevated | 1889 Elevated | 1676 Elevated | 1542 Elevated |
| D-Dimer ( ng FEU/mL) (<0.5) | 8.4 Elevated | 9.2 Elevated | 8.4 Elevated | 7.8 Elevated | 7.9 Elevated |
| RT-PCR | Negative | Negative | Negative | Negative | Negative |
| Covid antibodies | Negative | Positive | Negative | Positive | Positive |
| ECHO- Coronaries | Normal | Dilated | Dilated | Dilated | Dilated |
| Xray | Normal | Normal | Normal | Normal | Normal |
| Treatment | | | | | |
| Inj. Methyl prednisolone | Yes | Yes | Yes | Yes | Yes |
| IV Immunoglobulin | No | Yes | Yes | Yes | No |
| Tab. Azithromycin | No | Yes | No | No | Yes |
| Cap. Doxycycline | Yes | No | Yes | Yes | Yes |
| Tab. Aspirin | Yes | Yes | Yes | Yes | Yes |
| Tab. Ivermectin | No | Yes | Yes | Yes | No |
| Mechanical ventilation | No | No | Yes | Yes | No |
| Shifted to ICU | No | No | No | Yes | No |
| Spo2 at admission | 95% | 96% | 96% | 94% | 98% |
| Spo2 at Discharge | 98% | 98% | 98% | 98% | 97% |
| Duration of Hospital stay | 15 days | 11 days | 16 days | 17 days | 14 days |
| Outcome | Recovered | Recovered | Recovered | Recovered | Recovered |

Note: Inj. Methyl prednisolone 2mg/kg OD for 5 days; Tab. Azithromycin 10 mg/kg/day OD for 5 days; Tab. Doxycycline 4mg/kg/day BD for 5 days; Tab. Aspirin 3mg/kg/day 6 weeks to 6 months; tab. Ivermectin 0.2mg/kg; Oxygen 2 litres/min.

## DISCUSSION

All five patients in this case series had contact with COVID-19 positive family members, which suggests that family-clustered onset of infection is common in pediatric age group similar to the case series done in Uttar Pradesh by Ritesh Kumar et al.[9] Elevated antibodies for SARS-CoV-2 were found in 40 % cases which is consistent with study done by Dhanalakshmi et al in Chennai reported 58% positive.[10]

MIS-C generally tend to occur in older children (reported median age 8years) in our study also showed similar age group with median age of 6 years.[11,12]

In this case series, predominant symptoms in all cases were, fever (100%), Conjunctivitis (100%), Mucocutaneous Rash (100%) and oral ulcers


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(100%); similar in the studies conducted in USA by Dufort Etal,[13] reported Fever (100%), Gastro intestinal symptoms (80%), Rash (60%), Conjunctivitis(56%) and also in another study done by Feldestein et al,[11] in 26 states of USA reported common presenting symptoms similar to our case series, Fever (100%),Gastrointestinal involvement(92%),Cardio vascular involvement(80%), Rash (59%),Conjunctivitis(55%). Other presenting symptoms were irritable in child (80%), refusal to feed, gastrointestinal symptoms like abdominal pain and vomiting (60%) anddiarrhea (20%).

Other less common presentation were cough 20%, dyspnea 20%, Bleeding manifestation 20%, decreased urine output 20%.

A meta-analysis done by Irfan O et al, which included 8455 children, The most common presenting symptoms were fever (63.3%), cough (33.7%), nausea/vomiting (20.0%) and diarrhoea (19.6%). Other symptoms reported were dyspnoea, nasal symptoms, and rashes, Kawasaki like presentation, conjunctivitis, fatigue, abdominal pain and neurological features consistent with our case series.[14]

Mean duration of hospital stay was 14.5 days; while other authors reported length of hospital stay ranging between 11.6 to 13.6 days.[15,16]

Elevated CRP and D-dimer levels were detected in four patients (66.6%) each, and serum ferritin in three patients (50%). These findings were consistent with the observations of Irfan O et al., who showed raised CRP in 54.2% to 66.3%, D-dimer in 35.2% to 51.0% and serum ferritin in 46.7% to 61.7% of their cases.[14] Thus, raised inflammatory markers are also found in paediatric COVID-19 patients.

Laboratory evidence of systemic inflammation, myocardial dysfunction, and coagulation activation among patients has been consistently reported across the currently available literature. Per the case definitions of MIS-C, inflammatory markers, including C-reactive protein (CRP),ferritin, procalcitonin, and serum interleukin-6, are expected to be significantly elevated. Feldstein et al. found 171 out of 186 total subjects had elevations in at least four inflammatory biomarkers.[9] High levels of D-dimer and fibrinogen characterized coagulation dysfunction in most patients. In addition, laboratory evidence of lymphocytopenia, neutrophilia, hypoalbuminemia, anemia, and thrombocytopenia was also common.

Although,cardiac dysfunction is the most commonly reported organ dysfunction,[13] a notable finding in our series was that a fewer number of children were identified to haveechocardiographic evidence of coronary artery changes (3/19,16%), Ramcharan et al. and Toubiana et al. found coronary artery abnormalities in 93% and 47% of patients studied respectively.[12,17]

Currently there is no consensus regarding management of children with MIS-C; although there has been a recently published review suggesting a treatment flowchart.[18] IVIG (2 g/kg) has been most commonly used as first line therapy with many children receiving additional high-dose steroids.[11] Nearly half of the children (42%) in this series received both IVIG and steroids, with a few children requiring a second dose of IVIG and one child needing additional immuno-modulatory medication. The role of aspirin in children with hyper inflammation without KD is not yet described, though it has been used by many in PIMS-TS.[19] Similar to standard KD treatment, intravenous immunoglobulin (IVIG) therapy was the most commonly reported treatment provided to patients (55–100%), followed by corticosteroids (10–96%).[11,18,19] Often leading to rapid recovery within a few days, several studies support IVIG and corticosteroids as viable options for anti-inflammatory treatment.

Unlike adult population, only few children infected with COVID-19 required ventilatory support.[18,20] consistent with our case series.

Despite potentially severe clinical manifestations, outcomes of MIS-C are generally favorable and most cases tend to improve within a few days of treatment in our study all cases had a good recovery. Our study had no mortality consistent with other studies where mortality rates are relatively low, with the current estimates at approximately 2%.[10,11] It may be because of the fact that children have less co-morbidity like diabetes mellitus, hypertension than adult population.

## CONCLUSION

MIS-C patients typically present with persistent fever, mucocutaneous signs, and raised inflammatory markers. However, MIS-C tends to affect older children (5 years old) and is distinguishable by more remarkable multi-organ involvement, particularly that of the gastrointestinal (GI) and cardiovascular systems. Supportive care leads to adequate recovery. As such children are less prone to develop moderate/ severe form of the disease than adults due to lesser incidence of co-morbidities and better recovery rate. MIS-C remains a multi-faceted disease and hence poses a difficulty for the treating clinician to decide on the course of its management. New guidelines keep on emerging as the disease evolves over time.

While seemingly rare and generally treatable, MIS-C is yet another challenge associated with the COVID-19 pandemic. Given the existing knowledge gaps, it remains challenging to predict which children may be at higher risk for MIS-C and, moreover, which will have poor outcomes. Because current studies support the idea that SARS-CoV-2 may act as a trigger or immune modulatory factor in MIS-C pathogenesis, mitigating the transmission of SARS-CoV-2 not only serves to prevent COVID-19 but also presents a likely effective strategy for MIS-C prevention until future research can elucidate the


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etiology, pathophysiology, and potential long-term consequences associated with this rare condition.

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