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Case Series

Clinical profile and outcome of multisystem inflammatory syndrome in children and adolescents related to COVID-19 in a tertiary care hospital

Shreyaben M. Mistry[1]*, Kathan P. Buch[2], Pankaj M. Buch[1]

[1]Department of Paediatrics, PDU Gov. Medical College, Rajkot, Gujarat, India
[2]GCS Medical College, Ahmedabad, Gujarat, India

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***Correspondence:**
Dr. Shreyaben M. Mistry,
E-mail: mistryshreya3@gmail.com

ABSTRACT

The pandemic of COVID-19 initially appeared to cause only a mild illness in children. The paediatric age group comprises only less than 7% of total COVID-19 worldwide. Multi system inflammatory syndrome in children (MIS-C) is a rare, but life-threatening complication of SARS-CoV-2 infection. We report a case series of 24 children with suspicion of multisystem inflammatory syndrome related to COVID-19 were assessed using diagnostic criteria established by ministry of health and family welfare, government of India using detailed history, clinical examination and relevant laboratory investigations. Among total 24 patients ranging from 23 days to 11 years with mean age of 4.5 years includes 10 patients (41.67%) presented with mild illness, 7 patients (29.12%) with persistent fever to Kawasaki disease (KD) like illness and 7 patients (29.12%) with fatal disease with MODS and shock. These children were managed as per guidelines with modifications for individual case if necessary and includes supportive management with main stays of IVIG and steroids. Three children died.

Keywords: SARS-CoV-2, MIS-C, COVID-19, KD

INTRODUCTION

The severe acute respiratory syndrome Corona Virus-2 (SARSCoV2) is a global pandemic caused by a novel Corona virus disease (COVID-19) affecting all age groups from neonates to older children. Since the onset of the pandemic, COVID-19 has caused mostly asymptomatic or minor infections in children with an overall incidence of 1.8-6.3%.[1] Many countries have reported increased number of systemic hyperinflammatory condition owing to COVID-19 which is being considered as a rare but severe complication of COVID-19 mimicking KD, but with a greater degree of cytokine storm, severity, and poorer outcome is termed as multisystem inflammatory syndrome in children (MIS-C) or pediatric multisystem inflammatory syndrome (PIMS) or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIM-TS). It usually occurs 4-6 weeks following the SARS-CoV2 infection.[2] The clinical spectrum ranges from mild disease with persistent fever to KD like illness or severe life-threatening condition with shock and MODS (multi-organ dysfunction) leading to death.[3]

CASE SERIES

We present a case series conducted at a tertiary care hospital in a prospective observational manner of 24 patients diagnosed with MIS-C. Children admitted with suspicion of Multisystem inflammatory syndrome related to COVID-19 were assessed using diagnostic criteria established by Ministry of health and family welfare, Government of India (18th June, 2021) using detailed history, clinical examination and relevant laboratory

investigations. We ruled out acute COVID-19 illness, KD and common tropical infections.[3]

Among 24 of them diagnosed with MIS-C 13 (54.2%) were female and 11 (45.8%) were male and with mean age was 4.5 years ranging from 23 days to 11 years. As described in Figure 1 all 24 (100%) of them presented with fever >38°C. Gastrointestinal symptoms (83%), mucocutaneous involvement (62.5%), respiratory distress (58.33%) and shock (16.67%) were the other features.

These children were then evaluated by tiered investigations. Tier-1 which includes CBC with MP, CRP, ESR, blood culture and investigations for linkage to COVID-19 which is history of COVID-19 RTPCR/rapid antigen positivity in past 2 to 6 weeks, history of close contact with recent COVID-19 infection or positive serology. Then tier-2 investigations were done in patients with tier-1 positive patients and patients presenting with shock/MODS which consists of but not limited to are cardiac profile, inflammatory markers and blood gases.

Elevated level of C-reactive protein more than 5 mg/dl was found in 23 (95.83%) of them. 20 (83.33%) patients had evidence of coagulopathy. 2-D Echo was done in only 12 patients due to limitation of facility revealed 4 patients having pericardial effusion, 1 patient having moderate cardiac dysfunction with mild PAH, another one had severe PAH with PDA with PFO. Ten patients had positive contact history for recent COVID-19 infection and 1 had history of COVID-19 RTPCR positive 4 weeks ago with high (100% pts) presence of SARS-CoV-2 antibodies.

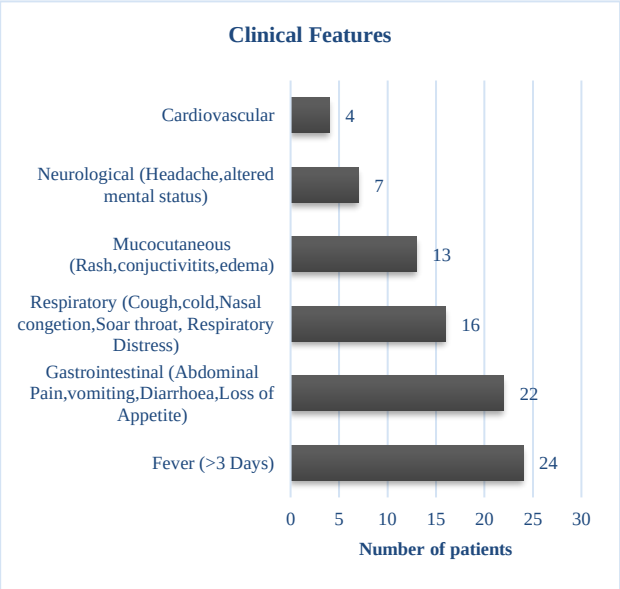

Figure 1: Clinical manifestations of MIS-C.

These children were managed as per guidelines with modifications for individual case if necessary. Children with MIS-C were classified by clinical severity into 3 categories: (1) MIS-C without shock (2) MIS-C KD phenotype (3) MIS-C with shock/MODS. The mainstay of treatment includes IVIg and steroids plus supportive management with iv fluid resuscitation, antibiotics, anticoagulants, ventilatory care and ionotropic support in patients presenting with shock with multidisciplinary team approach. Out of total 24 patients 13 were given MPS alone, 4 were given IVIG and 4 were treated with both. 4 children needed ventilatory support and 6 patients (25%) was given ionotropic support for shock. Mean (range) duration of stay was 13.75 (4-46 days) days. Three children died.

Table 2: Laboratory findings and investigations.

Parameters	Value-mean (Range)
Hb (gm/dl)	10.12 (2.6-15.8)
Total WBC count (cells/cumm)	14,741.67 (200-43000)
CRP (>5 mg/dl)	22.42 (0.5-317)
ESR (>40 mm in 1 hour)	74.58 (5-170)
Procalcitonin (ng/ml)	3.76 (0.079-35.6)
Neutrophils (%)	61.75 (30-93)
Lymphocytes (%)	35.38 (4-68)
Platelets (cells/cumm)	2,30,166.66 (24,000-5,66,000)
SGPT (IU/L)	48.46 (12-242)
D-dimer (ng/ml)	2,348.29 (520-4800)
Ferritin (ng/ml)	482.59 (80.63-1897)
LDH (IU/L)	444.95 (13-1512)
CKMB (IU/L)	45.86 (7-250)
Creatinine (mg/dl)	0.66 (0.4-3.1)
Sodium (mmol/L)	136.6 (124-152)
Troponin-I	Negative in all pts
PT (second)	21.1 (13.5-56.3)
APTT (second)	46.46 (18.1-444.3)
INR	1.52 (0.9-4.44)

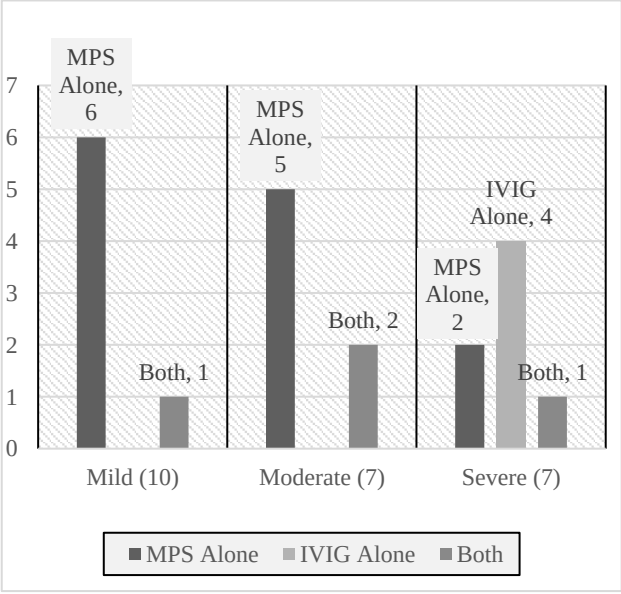

Figure 2: Clinical severity and treatment.

DISCUSSION

At the end of April 2020, while over 3 million SARS-CoV-2 infections were reported worldwide, a relative sudden emerge of children presenting a severe hyperinflammatory disorder with multisystem involvement, prompted an international alert. Noteworthy, during the first 4 months after the initial reports, more than 950 individual cases with PIMS-TS/MIS-C have been reported in scientific literature, and, subsequently were systematically reviewed.[4] Currently, several countries are still struggling with widespread SARS-CoV-2, requiring continuous and evidence-based updates on the COVID-19 spectrum, in particular concerning complicated disease courses. In this context, we performed this study of PIMS-TS/MIS-C to appropriately the characterize its presentation and prognosis.

Our study is reporting prospective case series of MIS-C syndrome with a total of 24 cases. Our knowledge about the epidemiology, pathogenesis, clinical spectrum, and associated laboratory abnormalities seen in MIS-C syndrome is still evolving.[5] The diagnostic criteria of MIS-C are constantly revised with time as more evidence is being generated.[5,6]

Our study identified that the affected age group was 23 days-11 years with mean age of 4.5 years. Sai et al in their study mentioned that most commonly affected age group was 6 to 12 years accounting for more than 50% of the study population.[7] This finding was in agreement with other similar published studies.[8-10] Our study also reveals that girls were affected more than boys. Similar finding was observed in the studies conducted by Sai et al who noticed male to female ratio of 1:1.9 and Dhanalakshmi et al who reported M:F ratio of 1:1.4.[7,11] However, most other studies showed male predisposition-Hoste et al (M:F-1.4:1 out of 928 cases), Goldfred et al (M:F-1.2:1 out of 570 cases), Sethy et al (M:F-3.2:1 out of 21 cases), Kaushik et al (M:F-1.6:1 out of 33 cases), and Sugunan et al (M:F-1.9:1 out of 32 cases).[4,8,9,13,14]

Out of 24 patients, one had history of RTPCR positive report and 10 patients had history of contact with COVID positive patient. Sai et al in their similar study conducted COVID RT-PCR in all patients and none were found to be positive. Rapid antigen test was positive in only one (1.3%) child in their study.[7] Fifty-four (69%) children had a history of contact with COVID positive cases. Other studies have shown RT-PCR positive in 19-31% of cases.[8,11,12] Sai et al noted a 2-6-week lag period for MIS-C presentation following COVID-19 infection or contact with COVID-19 case.[7]

The most common presentations were fever (100%), GI symptoms (91.66%) and respiratory symptoms (66.7%). Systematic review and meta-analysis conducted by Williams et al shows that Fever was the most commonly reported symptom (96%) in majority of studies.[14] Gastrointestinal (GI) symptoms (abdominal pain, nausea/vomiting, and diarrhoea) were noted in 86% of patients in all except two studies.[14]

Mean values of total WBC count, CRP level, ESR, procalcitonin, D-dimer, S. Ferritin, LDH, CKMB, prothrombin time level, activated partial thromboplastin time (aPTT), INR were elevated in our study while mean value of haemoglobin was below normal. Krishna Sai et al in their study found leucocytosis, high N/L ratio and thrombocytopenia in 45%, 20%, and 37% of patients respectively, C-reactive protein (CRP) was elevated in 58 (74%) patients while 38 (48%) had elevated ESR.[7] They also noted that serum ferritin, d-dimer, and LDH were elevated in 21%, 34%, and 5% respectively. In contrast, elevated CRP, ferritin, and d-dimer were found in a higher proportion of children in the reported literature.[14] Fifty-four percent of patients had biochemical evidence of hepatic dysfunction as evidenced by elevated SGOT, SGPT, or both, similar to a study published from South India.[8]

Systematic review and metanalysis conducted by Hoste et al reported that increased inflammatory markers were frequently documented, including C-reactive protein (CRP; median 249 mg/l [IQR 173-322] in single cases), ferritin (910 µg/l [457-1521]), and interleukin.[4] They also found that although white blood cell counts were frequently increased (12,800/µl [9150-20,075]), lymphocytopenia was common (831.5/µl [510-1157.5]).[4] Besides inflammatory parameters, coagulation markers were substantially upregulated, including d-dimers (3750 ng/ml [1946-6896]) and fibrinogen (640 mg/dl [504-800]) as reported by the systematic review. Furthermore, myocardial injury markers such as troponins (188 ng/l [60-614]) and brain natriuretic peptide (BNP) (median 1619 pg/ml [424-3325]) were often elevated.[4]

We used methyl prednisolone, antibiotics and IVIg as the first line of treatment followed by anticoagulants and inotropes. Though IVIg, steroids, anticoagulation, and aspirin are the mainstay of therapy in MISC syndrome, there is limited evidence to support their use. Due to the striking similarities of this syndrome with KD the same treatment is being recommended for MIS-C as well.[4,5,14]

The main limitation of this study is the small sample size and lack of follow-up. Long-term follow-up can throw more light on chronic complications of MIS-C in children.

CONCLUSION

MIS-C patients present with varied clinical features. The treatment is dependent on the severity of the disease and has been evolving with the availability of a wide range of therapeutic options. Outcome is better with early diagnosis and prompt treatment. In our setup when a child presents with fever with symptoms defined in

diagnostic criteria and raised inflammatory markers there should be high suspicion of MIS-C.

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