

Clinico-epidemiological profile of paediatric MIS-C patients presenting in a tertiary care hospital of India

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ABSTRACT: **Introduction:** MIS-C (multisystem Inflammatory Syndrome in Children) has a varied clinical presentation and range from symptoms like fever, loose stools or can present with life-threatening myocardial dysfunction and shock. **Methods:** Cross sectional observation study done in June and July of 2021 in a tertiary care hospital of North India and clinic-epidemiological profile of children with MIS-C was studied. **Result:** Fever was the most common symptom that was recorded (100%) followed by gastrointestinal symptoms (80%). All of them presented with raised markers of acute inflammation (CRP, D-Dimer etc). Cardiovascular complications included shock (36%) with LV dysfunction (22%), myocarditis (20%), coronary dilatation (16%), and pulmonary edema (10%). 20% of them had rashes. Bleeding was seen in 12% of the cases. Few patients had rare presentation like ileus, cardiac tamponade and were later diagnosed as MIS-C and also showed improvement after the treatment. **Conclusion:** Patients with such clinical features without evidence of tropical infection should be kept as a possibility of MIS-C.

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Keywords: MIS-C, COVID, SHOCK

INTRODUCTION

The global pandemic of SARS CoV-2 caused around 1 million deaths out of the reported 37 million cases in the world and majority were adults (1). In children who are COVID positive, a milder disease is the usual presentation (2) (3). However, a new entity was increasingly diagnosed in children as a complication of post corona virus infection. The earlier hypothesis that COVID-19 was always milder in children was challenged by emergence of post corona virus inflammatory syndrome in infants and children. This rare but lethal disease entity was reported from the United Kingdom, Italy, and New York City. The exact mechanism of pathophysiology is not well established. A post infectious abnormal immune response is widely suggested. It has some similarity with Kawasaki Disease and Macrophage Activation Syndrome. It is challenging to differentiate MIS-C from Kawasaki Disease and Toxic Shock Syndrome as main clinical and laboratory features overlaps. KD is a self-limiting condition

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that presents with high fever of more than 5 days and 4 of the following 5 principal features classifies classic KD: (i) non purulent conjunctival injection, (ii) rash, (iii) erythema and edema of the hands and feet, (iv) cervical lymphadenopathy, (v) oral mucosal changes. It may cause severe complications including coronary aneurysm, myocardial dysfunction and thromboembolism. The diagnosis of incomplete KD includes fever with 2-3 of the principal features(4). TSS is a severe disease characterised by fever, rashes, shock, diarrhoea (5).

As more cases emerged globally, MIS-C is recognised by CDC and WHO and case definition has been published (6,7). Management consists of supportive treatment in conjunction with anticoagulation, steroids and immunoglobulins (7).

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AIM AND OBJECTIVE

To observe the clinical spectrum and laboratory parameters of mild and severe cases of MIS-C. To check the effect of steroids and immunoglobulins (XXX) on laboratory parameters.

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MATERIAL AND METHODS

This was a cross-sectional observational study done from June 2021 to July 2021 in a tertiary care centre in North India. The clinical findings, laboratory parameters, echocardiography and treatment strategies of 50 patients fulfilling the WHO criteria of MIS-C were recorded and analysed.

The WHO case definition of MISC (7) was used as any child (0-18years) with fever of ≥ 3 days along with any two of the following:

- 1) Rash or non-purulent conjunctivitis or erythema/edema of hands and feet
- 2) Shock
- 3) Myocardial dysfunction or coronary involvement or elevated Troponin or ProBNP.
- 4) Gastrointestinal symptoms
- 5) Coagulopathy

Along with raised inflammatory markers like CRP/ESR/Procalcitonin, no evidence of endemic infections and evidence of a positive RTPCR/Antibody/Antigen/Contact.

All patients underwent various blood tests like Complete blood count, Renal function test, Liver function test, CRP, ESR, D-dimer, PT-INR, Electrolytes, blood culture, ECG,

Echocardiography and in a few patients ProBNP/Troponin was done whenever diagnosis was not clear. All the patients were treated according to the WHO guidelines and post treatment parameters like defervescence, D-Dimer, CRP, ECG and Echocardiography were recorded.

RESULTS

A total of 50 patients were observed and enrolled in the study. Among them 44% had severe illness in the form of shock, myocarditis, bleeding and coronary involvement. The number of females diagnosed as MISC were 62% and males were 38%. History of contact with COVID positive patient was seen in 11 patients. All the patients were COVID RT-PCR negative. Covid antibody (IgG and IgM) positivity was seen in 43 patients (86%). The mean antibody titre was 8.9 ± 2.3 (more than was considered as positive). It was seen that 18 patients (36%) were positive for Widal test.

Fever was the most common symptom seen in MISC patients (100%) followed by diarrhoea (80%), shock (36%), LV dysfunction (22%), myocarditis (20%), rash (20%), coronary dilatation (16%), bleeding (12%) and pulmonary edema (10%).

The mean haemoglobin (gm/dl), Total leucocyte counts, DLC and platelet were 8.99 ± 2.2 , 6889 ± 1480 , $N63 \pm 13$, $L33 \pm 14$ and $1.6 \text{ lac} \pm 1360$ respectively. The mean CRP (mg/dl) was 91.6 ± 7.1 which improved to 22.7 ± 2 after 72 hrs of treatment. The mean CRP among mild and severe cases was 82.7 ± 7 and 103 ± 8 . The mean ESR (mm/hr) was 38.9 ± 2.4 . The mean ESR in mild and severe cases was 31.1 ± 20.2 and 41 ± 29.3 respectively. Mean D-dimer levels (ng/ml) among the total cases was 4144 ± 308 which improved to 1577 ± 211 after 72 hours of treatment. In mild and severe cases, it was 3319 ± 492 and 5193 ± 349 respectively. The average value for INR was 1.34 ± 0.3 . Serum sodium was about 130 ± 5.1 in all the cases where as in mild and severe cases it was 133.5 ± 5.2 and 128 ± 5.4 .

IVIg was given in 19 out of 22 severe cases and in 11 out of 28 mild cases of MISC. While all the severe cases (22) were treated with pulse dose of methyl prednisolone (10-30 mg/kg/day for 5 days followed by tapering over 2-3 weeks), only 1 mild case of rashes was given pulse dose. Around 27 (out of 28) mild cases were directly started with low dose methyl prednisolone (1-2 mg/kg/day for 2-3 weeks). Enoxaparin was given in 8 patients and out of them 7 were severe cases. Aspirin was advised for 18 patients who had LV dysfunction or coronary involvement or high level of D-Dimer at or above 5 times normal. Empirical

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antibiotics were given in 45 patients including all the severe cases. Forty-eight patients were discharged satisfactorily after 5-7 days of admission. None of the cases presented with significant residual cardiac involvement after one month on follow up.

DISCUSSION

The second lethal surge of SARS Cov-2 was seen from mid April 2021 in adult patients. As seen during the first wave the younger population of infants and children seemed to be relatively unaffected initially (around 1% of admitted patients) with the disease severity ranging from asymptomatic to mild in most cases. However after around 4-6 weeks of infection with covid, we witnessed a rapid rise in children admitted for a post covid inflammatory disease involving multiple organs with features overlapping with Kawasaki disease and toxic shock syndrome. Initially the cases presenting to us were severe (44%) and required IVIG, enoxaparin and pulse Methylprednisolone. Later, we witnessed mostly mild cases of MISC (56%) easily manageable with oral low dose steroids. All the MIS-C cases with myocarditis, LV dysfunction, coronary artery dilatation, shock, pericardial effusion and bleeding were considered severe.

The age of the patient was found to have no correlation with the severity of the disease as mean age in mild and severe MISC was 5.28yrs and 6.86yrs respectively. Our lower age limit was 1 month while the upper age limit was 14 years. Other studies such as Radia et al(8) had the median age as 8.6 years (range 3 months–20 years).

Cases were seen in infants as young as one month of age and these were clinically active with normal feeding apart from high grade fever. It was found that females (62%) were more prone to develop features of MISC than males (38%) and this difference was statistically significant. However, gender has no correlation with the severity. There was no significant association found between the titres of COVID antibody and the severity of MISC. Almost one third (36%) patients were false positive for WIDAL and all of them were positive with high titres of COVID antibodies.

In our study it was found that the most common symptom seen in all the patients was high grade fever which drastically responded to 1-2 days treatment with steroids or IVIG. This corresponded to the 58-patient study by Whittaker (9). This was followed by diarrhoea (80%) which was easily managed with oral rehydration solution which was in congruence with studies published by Cheung (10) and Dufort et al (11) which reported 88% and 80%

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prevalence of gastrointestinal symptoms and the systematic review by T. Radia et al (8). Shock was seen in 36% of cases and was warm vasodilatory often requiring nor- adrenaline unlike the British study and the New York study which had a high prevalence of 63% and 47% respectively (11). LV dysfunction (22%) and myocarditis (20%) also complicated early recovery.

The classical rash was seen in 20% of cases which is lower than 71% prevalence observed by Cheung (10). 16% patients had coronary dilatation which is similar to the Italian and British studies and with 20% and 13% prevalence of aneurysm (9,12). Bleeding in form of upper gastrointestinal, epistaxis and haematuria was seen in 12% and pulmonary edema in 10% cases.

Elevated inflammatory markers like CRP, ESR, Procalcitonin were seen in all the patients of MISC.

In our study we have seen a few atypical presentations. Three infants (2,3 and 4 months) presented with high grade fever and paralytic ileus with markedly raised D dimer and CRP. After giving IVIG 2gm/kg, they showed drastic response in terms of resolving of fever and ileus.

Two babies of 1month each had high grade of fever, mottling and mild LV dysfunction with investigations supportive for MISC and no alternate diagnosis, recovered completely with treatment with IVIG and low dose steroid. . This was in conjunction with the definition of Fetal inflammatory response syndrome and also study by Kyra et al (13) that concludes that multisystem involvement with increased CRP is common in FIRS.

There were 2 children who were admitted for MISC (fever, diarrhoea, positive lab investigations) and later had seizures. MRI brain was suggestive of Tubercular meningitis. There were 2 children with pericardial effusion causing cardiac tamponade. They were fitting in MISC criteria and were given IVIG and Methylprednisolone and pericardial tap was done. Later the fluid study was suggestive of Tuberculosis (CBNAAT positive). Hence, there might be a possibility of reactivation of latent tuberculosis post COVID MISC and it warrants further studies.

References:

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UNDER PEER REVIEW

Table1. Baseline Parameters of study subjects

Parameter		Mild MISC	Severe MISC	Total	p-Value
CASES		28(56%)	22(44%)	50	0.680
AGE (mean years)		5.28±2.34	6.86±2.24	5.97±2.20	0.730
GENDER	Males	11(57.9%)	8(42.1%)	19	0.430
	Females	17(54.8%)	14(45.2%)	31	0.782
COVID CONTACT	Present	5(45.5%)	6(54.5%)	11	0.880
COVID RTPCR	Negative	28(56%)	22(44%)	50	0.630
COVID ANTIBODY	Positive	26(60.5%)	17(39.5%)	43	0.590
COVID ANTIBODY MEAN TITRE		9.0±2.3	8.7±2.7	8.9±2.3	0.450
WIDAL POSITIVE		6(33.4%)	12(66.6%)	18	0.287

Table 2. Clinical spectrum

Parameter	Mild MISC	Severe MISC	Total(50)
FEVER	28(56%)	22(44%)	50(100%)
RASH	4(40%)	6(60%)	10(20%)
SHOCK	0(0%)	18(100%)	18(36%)
DIARRHOEA	21(52.5%)	19(47.5%)	40(80%)
BLEEDING	2(33.3%)	4(66.7%)	6(12%)
MYOCARDITIS	0	10(100%)	10(20%)
LV DYSFUNCTION	0	11(100%)	11(22%)
PULMONARY EDEMA	0	5(100%)	5(10%)
CORONARY DILATATION	0	8(100%)	8(16%)

Table 3. Laboratory parameters

Parameter	Mild MISC	Severe MISC	Total
Hb(gm/dl)	8.78±1.3	9.28±2.6	8.99±2.2
TLC	6983±1732	6736±1464	6889±1480

NEUTROPHILS/ LYMPHOCYTES	N61±14 L35±14	N65±12 L31±13	N63±13 L33±14
PLATELETS	171750±1380	145818±1350	160340±1360
CRP	82.7±7	103±8	91.6±7.1
CRP AFTER Tt	22.2±2.2	23.4±1.6	22.7±2
ESR	37.14±20.2	41±29.3	38.9±24
Ddimer	3319±492	5193±349	4144±308
Ddimer after Tt	1430.7±199.9	1763±228	1577±211
INR	1.29±0.2	1.4±0.4	1.34±0.3
Sodium	133.5±5.2	128± 5.4	130±5.1
Potassium	3.7±0.5	3.3±0.7	3.5±0.6

Table 4. Treatment and outcome

Parameter	Mild MISC	Severe MISC	Total
IVIG	11	19	30
Methylprednisolone Pulse dose	1	22	23
Methylprednisolone low dose	27	0	27
Enoxaparin	1	7	8
Aspirin	10	8	18
Empirical antibiotics	23	22	45
Outcome	Discharged	28	48
	Expired	0	2