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Clinico-epidemiological Profile of Multisystem Inflammatory Syndrome in Children

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Introduction: MIS-C (multisystem Inflammatory Syndrome in Children) has been reported as a complication of post COVID infection in paediatric age group. The presentation of this syndrome includes constellation of clinical features. This study aims to inquire about the incidence of these symptoms in the clinical setting.
Methods: Cross sectional observation study in a tertiary care hospital of North India and clinic-epidemiological profile of children with MIS-C was studied.
Results: Fever was the most common symptom (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 Left Ventricular dysfunction (22%), myocarditis (20%), coronary dilatation (16%), and pulmonary edema (10%). Rash was noticed in

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20% of the cases and bleeding was seen in 12% of the cases. Few patients had other rare presentations also.
Conclusion: Patients with such clinical features without evidence of tropical infection should be kept as a possibility of MIS-C.

Keywords: MIS-C; COVID; SHOCK.

1. 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 postcoronavirus 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 (KD) 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 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 Centre of Disease control (CDC) and World Health Organisation (WHO) and case definition has been published [6,7]. Management consists of supportive treatment in conjunction with anticoagulation, steroids and immunoglobulins [7].

2. AIM AND OBJECTIVE

To observe the clinical spectrum and laboratory parameters of mild and severe cases of MIS-C. To check the subsequent effect of therapy on laboratory parameters.

3. MATERIALS AND METHODS

This was a retrospective 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. Sampling was done on the basis of convenience as all the patients who were admitted in the unit in this period were part of the study.

The WHO case definition of MISC [7] was used as any child (0-18years) with fever of ≥3days 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.All the MIS-C cases with myocarditis, LV dysfunction, coronary artery dilatation, shock, pericardial effusion and bleeding were considered severe.

Sample size was not calculated on the basis of past studies as the data was scare and very infrequent reporting through articles in publication. Since limiting criteria was the number of cases, hence we enrolled 95% of the cases that presented to us during three months interval.

Categorical data were compared using Chi-square test. Continuous variables such as age, anthropometric data etc were compared using independent sample t-test. Significance was considered at a p-value below 0.05. All statistical analysis were done using IBM SPSS Statistics version 26 software (IBM USA).

4. RESULTS AND DISCUSSION

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 girls diagnosed as MISC were 62% and boys were 38%. The 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). The age of the patient had no correlation with the severity of the disease as mean age in mild and severe MISC was 5.28yrs and 6.86yrs respectively. It was found that females (62%) were more prone to develop features of MISC than males (38%) and this difference was statistically significant. However, the severity of the disease has no correlation with the gender. History of contact with COVID positive patient was seen in 11 patients. All the patients were COVID reverse transcriptase polymerase chain reaction (RT-PCR) negative. Covid antibody (IgG and IgM) positivity was seen in 43patients (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 and all of them were positive with high titres of COVID antibodies. Elevated inflammatory markers like CRP, ESR, Procalcitonin were seen in all the patients of MISC. There was no significant association found between the titres of COVID antibody and the severity of MISC.

The mean haemoglobin(gm/dl), Total leucocyte counts, differential leucocyte counts and platelet were 8.99±2.2, 6889±1480, N63±13 L33±14 and 1.6lac±1360 respectively. The mean C-reactive protein (mg/dl) was 91.6±7.1 which improved to 22.7±2 after 72hrs 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 international normalised ratio (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 were treated with pulse dose of methyl prednisolone (10-30mg/kg/day for 5days followed by tapering over 2-3weeks), 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 (1-2mg/kg/day for 2-3weeks). 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 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. Initially the cases presenting to us were severe (44%) and required IVIG, enoxaparin and pulse Methylprednisolone. Later mild cases of MISC (56%) were easily manageable with oral low dose steroids.

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

Table 1. 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	20	48
	Expired	0	2	2

prevalence of aneurysm [9,12],. Bleeding in form of upper gastrointestinal, epistaxis and haematuria was seen in 12% and pulmonary edema in 10% cases. In this 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 C-reactive proteins is common in Fetal Inflammatory Response Syndrome (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.

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. In this 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.

5. CONCLUSION

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, there was 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. Fever followed by gastrointestinal infection was most frequently encountered symptomology in these patients. All these cases needed detailed cardiac evaluation due to high incidence of cardiac complication. All the cases presented with raised acute phase reactants. In high incidence setting if future pandemic occurs, MISC should be kept as a differential diagnosis if these symptoms were present and investigation of endemic/tropical infection comes out to be negative. This study has its own limitation in the form of cross-sectional study without a comparable group. Furthermore, these findings should be also checked in multi-centre based studies and a meta-analysis of these data is needed to further elaborate the epidemiological and clinical findings in MISC.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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