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Original Research Article

Clinical profile and outcome of patients admitted as multisystem inflammatory syndrome in children in a paediatric tertiary care hospital of North India

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ABSTRACT

Background: Severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) infection can lead to multisystem inflammatory syndrome in children (MIS-C). This study was conducted to study epidemiology, clinical profile, treatment strategies associated in children with MIS-C in a medical college hospital in North India.
Methods: This is an observational study of children with MIS-C, admitted to paediatric intensive care unit between 01 March 2021 and 31 August 2021 during the second wave of SARS-CoV-2 infection in India. Demographic and clinical data including laboratory parameters, treatment regimens, and outcomes were collected and analyzed.
Results: Out of the 37 children presenting with MIS-C, sixty two percent patients were male and 37% were female patients. Fever was the most common symptom seen in all patients. Gastrointestinal system dysfunction was the most common systemic involvement seen in 72% patients. Anaemia was the most common sign of haematological dysfunction. Shock was seen in 37.84% patients and myocarditis was seen in 24.32% patients. Inflammatory markers were elevated in majority of children. Vasoactive medications were required in 14 patients. Eighteen patients required respiratory support of which 17 received non-invasive ventilation and only 1 patient required invasive mechanical ventilation. Methyl prednisolone and intravenous immunoglobulin (IVIG) were used in the majority of patients. No patient required remdesivir. Thirty-six patients were discharged home with a median duration of 4 days in paediatric intensive care unit (PICU) and hospital stay of 10 days, only 1 (2.7%) patient died during the treatment.
Conclusions: Combination of steroid and IVIG for the treatment of MIS-C, especially with shock and MODS reduce the duration of PICU stay than treated with steroid alone.

Keywords: COVID-19, Multisystem inflammatory syndrome in children, SARS-CoV-2

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a dreaded complication related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is seen more often in paediatric age group than in adults.[1] Although clinical course of COVID-19 is milder in children compared to adults, this paediatric inflammatory disease often leads to multiorgan failure and shock requiring admission to intensive care units. Clinical presentation is variable, with most centres reporting significant gastrointestinal (GI) symptoms, cardiac disease, and mild or absent respiratory symptoms, and variable incidence of rash, red eyes, and oral mucous membrane changes. It is still unclear if this is a post infectious complication or a primary complication of infection with SARS-CoV-2, however, initial epidemiologic descriptions are highly suggestive of a correlation.[2]

This observational study was conducted to assess the clinical profile and treatment outcome of patients admitted as MIS-C.

METHODS

This prospective observational study was conducted in paediatric intensive care unit (PICU) of department of paediatrics, Government Medical College, Jammu, a tertiary care hospital in North India. The hospital institutional review board approved the study with waiver of informed consent taken from patient caretakers. Children admitted with MIS-C aged 1 month to 17 years of age from 01 March 2021 to 31 August 2021 were included in the study. Patients who fulfilled the center of disease control and prevention (CDC) criteria for diagnosis of MIS-C during the study period were included in the study. MIS-C was defined in an individual <21 years presenting with a fever for >24 hours, laboratory evidence of inflammation, and evidence of severe illness requiring hospitalization, with multisystem involvement of >2 organs (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); and no alternative diagnoses; and positive recent SARS-CoV-2 infection or exposure to a suspected or confirmed COVID-19 case.

Exclusion criteria

Patients who had no evidence of exposure to recent SARS-CoV-2 and infective causes like dengue, enteric fever, leptospirosis, scrub typhus and bacterial sepsis were excluded by appropriate investigations.

Sampling

All those patients who were admitted for MIS-C during the study period of six months were included in the study.

Inflammatory markers done were C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), procalcitonin, ferritin and D-dimer. CRP was repeated in each patient 48 hours after administration of immune-modulator to monitor response to therapy. Coagulogram was also done to see coagulopathy. SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) was done in all patients, and SARS-CoV-2 antibody testing was also done using Vitros CoV2T. Shock was defined when a patient required more than 20 ml/kg of intravenous (IV) fluid resuscitation or inotropic support to maintain blood pressure above the 5th centile. Echocardiography was done in all patients with MIS-C and all patients were subsequently seen by a cardiologist to look for coronary artery status and cardiac dysfunction. Study variables were documented using pre-designed proforma including patient demographic details, symptoms and clinical signs, laboratory parameters, type of immune-modulator used, duration of hospital stay, presence of shock, need for inotropic support, duration and type of respiratory support, coronary artery changes at 2 weeks follow-up and outcome. Patients who were treated with methylprednisolone received pulse dose of 30 mg/kg (maximum 1 gram) once daily for 3 days followed by oral prednisolone at 2 mg/kg for 2 weeks. Steroid was tapered and stopped over the next 2-3 weeks. Children who were treated with IVIG received 2 g/kg as a continuous infusion over 8-12 hours. CRP and D-dimer were repeated on the third and seventh day after the start of IVIG or methylprednisolone. Children with treatment failure with pulse methylprednisolone were treated with IVIG. All patients were followed up at two weeks after discharge. All patients with shock were started on low molecular weight heparin (LMWH) at prophylactic dose. Children on LMWH were transitioned to low dose aspirin once liver enzymes normalized and platelet count increased to more than 80×109/l. Anti-inflammatory dose of aspirin (50 mg/kg) was given in refractory MIS-C with KD like presentation.

The data entry was done in the Microsoft excel spreadsheet and the final analysis was done with the use of statistical package for social sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0.

RESULTS

We included and analysed 37 children with MIS-C who met the CDC case definition of SARS CoV-2 infection based on our inclusion criteria. Sixty two percent (23) of study patients (37) were male and 37 % were female patients. Median age was 7 (IQR 3-10) years. Median weight of patients was 25 kg (IQR 17 to 30). Family history of COVID-19 was seen only in 16% (6) of MISC patients while as previous history COVID-19 was seen only in 5% (2) patients. Demographic details are showed on Table 1 and Figure 1.

Table 1: Distribution of demographic characteristics of study patients.

Demographic characteristics	Frequency	Percentage
Gender		
Female	14	37.84
Male	23	62.16
Age (years)		
Mean±SD	7.18±4.3	
Median (25th-75th percentile)	7 (3-10)	
Range	1-16	
Weight (kg)		
Mean±SD	26.05±13.66	
Median (25th-75th percentile)	25 (17-30)	
Range	8-70	

Fever was the most common symptom seen in 10% of patients followed by gastric upset (loose motion and/or

vomiting) (72%), redness of eyes (43%) and skin rash (32%). Gastrointestinal system dysfunction was the most common systemic involvement seen in 72% (27) followed by pneumonia 62% (23) and haematological involvement in 51% (19) patients (Table 2).

Table 2: Distribution of systemic involvement of study subjects.

System involvement	Frequency	Percentage (%)
Pneumonia	23	62.16
Haematology	19	51.35
Gastrointestinal	27	72.97
Mucous membrane	5	13.51
Nervous	2	5.41
Coagulopathy	12	32.43
Skeletal	3	8.11
Lymphadenopathy	3	8.11

Laboratory findings

Laboratory test results are presented in Table 3. Anaemia was the most common sign of haematological dysfunction followed by thrombocytopenia and leucocytosis. Shock was seen in 14 (37.84%) patients and myocarditis was seen in 9 (24.32%) patients. Salmonella serology was positive in patients and all these showed negative blood cultures for *Salmonella*.

Table 3: Distribution of laboratory parameters of study patients.

Lab investigations	Frequency	Percentage (%)
Anemia	20	54.05
Leucocytosis	18	48.65
Lymphocytosis	8	21.62
Thrombocytopenia	12	32
Coagulopathy	17	45.95
Transaminitis	5	13.5
Hyponatremia	6	16.22
Raised CRP	36	97.30
Raised ferritin	29	78.38
Raised ESR	14	37.84
Raised LDH	7	18.92
Raised D-dimer	31	83.78
Raised procalcitonin	13	35.14
Positive RAT for SARS-CoV-2	3	8.1
Positive RTPCR for SARS-CoV-2	4	10.08
Positive antibodies for SARS-CoV-2	30	81

Markers of inflammation were raised in majority of children. CRP was raised in 97% patients, ESR in 37%, ferritin in 78%, LDH in 18%, D-dimer in 83% and procalcitonin in 35% patients. Echocardiograms were performed in 26 patients of which 10 (27%) had depressed left ventricle ejection fraction, 1 (2.7%) had abnormal coronaries.

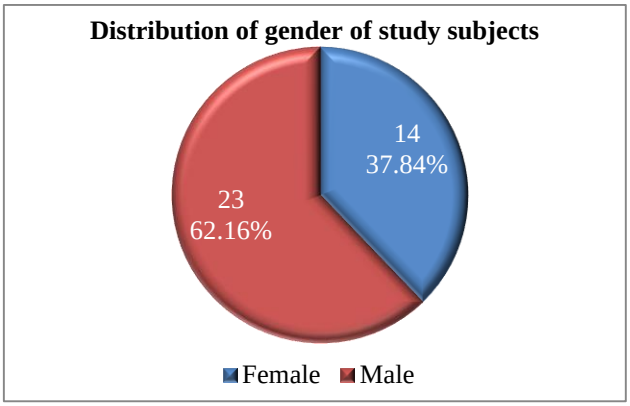

Figure 1: Distribution of gender of study patients.

Treatment

Medical therapies used are presented in Table 4. Nineteen (51 %) patients presented in shock and received fluid resuscitation. Vasoactive medications were used in 14 (37.84%) patients of which 10 (27%) required single inotrope, 4 (10%) required 2-3 inotropes. Eighteen patients (48%) required respiratory support of which 17 (45.9%) received non-invasive ventilation: 5 (13.5%) requiring oxygen by venture mask, 12 (32.4%) required non rebreather mask, only 1 patient required invasive mechanical ventilation. Both steroid and IVIG were used in the majority of patients (28/37, 75.6%), only steroids 18.9% (7/37) patients. steroid given was IV methyl prednisolone followed by oral prednisolone. Aspirin was started in 21 (56%) patients and heparin (LMW) in 27 (72%) patients. No patient required remdesivir. Empiric antibiotic cover was given in all patients.

Table 4: Distribution of management of study subjects.

Management	Frequency	Percentage (%)
Non-invasive respiratory support	17	45.95
Inotropes	14	37.84
Steroids	35	94.59
LMWH	27	72.97
Aspirin	21	56.76
IVIG	28	75.68
Remedesvir	0	0.00

Outcome

Thirty patients (81%) required paediatric ICU (PICU) admission and 7 patients were managed in the emergency ward. Among ICU admission, 13 (35%) patients had ICU stay of 4-5 days, 10 (27%) patients required 2–3 days of stay, 7 (18.9%) required stay for 7–10 days. Thirty-six

were discharged home with a median duration of 4 days in PICU and hospital stay of 10 days, only 1 (2.7%) patient died during the treatment.

DISCUSSION

In our study, incidence of MIS-C was higher in males than females (62% versus 37%), similar to that observed in other multicenter studies of MIS-C in the United Kingdom and the United States.[3,4] Biological differences (genetic and epigenetic) between males and females may affect the immune response to SARS-CoV-2 infection.[5] Median age of presentation in our study was 7 years consistent with the findings of study by Soma et al.[6]

In our study population, only 18% of the patients were positive for COVID antigen while as 81% patients (30) were positive for COVID antibody. Four patients tested positive for SARS-CoV-2 by RT-PCR, which generally reflects an acute phase of the infection, although the virus or its fragments may be detected for longer periods in some patients and could be responsible for these results, outside the classical period of positivity of the acute phase of COVID-19.

Clinical features of MIS-C can vary but do overlap with other paediatric inflammatory conditions including Kawasaki disease (KD).[7] The high frequency of gastrointestinal symptoms, the low prevalence of severe respiratory compromise, and the lesser degree of mucosal involvement seen in our study characterizes MIS-C as a distinct entity, unrelated to classic KD.[8,9] Consistent with the diagnosis of MIS-C, multiple inflammatory markers were elevated. Examining the trends of some of these values may provide biological insight into the disease or may serve as potential predictors of MIS-C outcomes.

Children in our study showed a significant elevation in all the inflammatory markers (CRP, PCT, D-dimer, and ferritin), all of which, showed a gradual reduction concurrent with clinical response. The elevation in these markers has been routinely reported in MIS-C cases across the globe.[10] Anaemia and hyponatremia were also common in our patients; however, these findings are also seen in KD.[11] Echocardiographic findings similar to those of KD were also common in this cohort. These findings are compatible with myocardial dysfunction and inflammation consistently described in MIS-C reports.[9-12] Its mechanism is not fully understood, but it may be related to micro vascular damage, stress cardiomyopathy (Takotsubo syndrome) and systemic inflammatory response syndrome.[13] Aspirin was used in all patients and initial dose ranging from 25 to 75 mg/kg/day which was changed to 3-5 mg/kg/day after 48 hours of afebrile period. The role of aspirin in the treatment of KD is well established and has been used in all patients with a phenotype similar to complete KD. Enoxaparin was also used in almost all patients since D-dimers were highly elevated in most of them. Children with MIS-C are at risk for thrombotic complications of multiple causes, due to a hypercoagulable state, possible endothelial injury, immobilization stasis, ventricular dysfunction, and CAA. For these reasons, antiplatelet and/or anticoagulation treatment is recommended, based on coagulation tests and clinical presentation.[13,14] Although there is no current evidence for the best management of MIS-C, guidelines from different organizations recommend treatment based on the clinical phenotype.[10,14] Combination therapy of steroid and IVIG was used in the majority of patients. Although children diagnosed with MIS-C often require intensive care treatment, studies have shown good outcomes and a low mortality rate.[5] Our study found similar outcomes, with only 1 death (2.7%), but with a similar length of PICU stay (median: 4 days) that had been reported in other cohorts.[5] Median PICU stay of 4 days points toward improvement in the majority of patients by day 3–5 and discharge from hospital by seventh day.

Limitations

Study was single-centered study done only over a short period of six months during second wave of SARS-CoV-2 in India. Sample size was also very small in this study.

CONCLUSION

Both steroids and steroid with IVIG for the treatment of MIS-C, especially with shock and MODS reduced the duration of PICU stay. Further interventional studies and clinical trials with larger sample sizes are required that can compare efficacy of various treatment modalities of MIS-C.

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

REFERENCES

1. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet. 2020;395:1771-8.
2. Bhat CS, Gupta L, Balasubramanian S, Singh S, Ramanan AV. Hyperinflammatory Syndrome in Children Associated With COVID-19: Need for Awareness. Indian Pediatr. 2020;57(10):929-35.
3. Panupattanapong S, Brooks EB. New spectrum of COVID-19 manifestations in children: Kawasaki-like syndrome and hyperinflammatory response. Cleve Clin J Med. 2020.
4. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr. 2020;224:141-5.

5. Mehta R, Joshi VH, Joshi P, Bhondve A, Otiv M, Udani S, et al. A multicenter study of clinical and biochemical profiles, treatments, and short-term outcomes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection from Western India. J Pediatr Crit Care. 2021;8:270-7.
6. Soma VL, Shust GF, Ratner AJ. Multisystem inflammatory syndrome in children. Curr Opin Pediatr. 2021;33(1):152-8.
7. Loscalzo S, Srinivasan V. COVID-19-associated multi-system inflammatory syndrome in children: Not "MIS-Cing" the wood for the trees! J Pediatr Crit Care. 2021;8:263-5.
8. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334-46.
9. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: A multicentre observational study. Lancet Child Adolesc Health. 2020;4:669-77.
10. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324:259-69.
11. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki disease: Novel virus and novel case. Hosp Pediatr. 2020;10:537-40.
12. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607-8.
13. Sperotto F, Friedman KG, Son MB, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: A comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180:307-22.
14. Kache S, Chisti MJ, Gumbo F, Mupere E, Zhi X, Nallasamy K, et al. COVID-19 PICU guidelines: for high- and limited-resource settings. Pediatr Res. 2020;88:705-16.

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