Clinical Profile and Outcome of Children Admitted with Multisystem Inflammatory Syndrome (MIS-C) in a Tertiary Hospital

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ABSTRACT

Background

Most children infected with SARS-CoV-2 infection, are asymptomatic or develops mild to moderate symptoms. Few weeks later, few children develops delayed hyper inflammatory syndrome known as Multisystem inflammatory syndrome in children (MIS-C).

Objective

To describe various demographic features of children with Multisystem inflammatory syndrome in children. To analyze common clinical presentation, clinical and laboratory markers of severity and outcome of children with Multisystem inflammatory syndrome.

Method

This study was prospective observational study conducted on children with Multisystem inflammatory syndrome in children. This was conducted in Department of Pediatrics of Nobel Medical College during 12 months period from July 2021 to June 2022. Basic demographic features, common clinical presentation in children with Multisystem inflammatory syndrome in children and its severity and outcome were analyzed. Independent sample t-test and chi square test was used for comparison of means and categorical variables. Logistic regression was done to assess the relationship between clinical variables and outcome.

Result

A total of 36 children were included in our study. Maximum number of cases were male (61.11%) and age group > 10 years (58.33%). Fever, gastrointestinal symptoms, shock and renal dysfunction were common clinical features. Children requiring mechanical ventilation had higher C-reactive protein (CRP), lower platelets, higher d-Dimer and lower ejection fraction. Vasoactive Inotropic score (VIS > 10) was associated with higher chances of mechanical ventilation and prolonged pediatric intensive care unit (PICU) stay. Mortality rate in our study was 5.55% and three children developed coronary aneurysm.

Conclusion

Multisystem inflammatory syndrome in children is life threatening illness following COVID 19 infection. Diagnosis and management of Multisystem inflammatory syndrome in children requires early suspicion and appropriate intervention to prevent mortality.

KEY WORDS

Covid 19, Multisystem inflammatory syndrome, Shock

INTRODUCTION

Children infected with SARS-CoV-2 virus, usually are asymptomatic or have mild to moderate infection. Some of these children, 4-6 weeks later develop a rare and delayed life threatening illness, named as Multisystem inflammatory Syndrome in Children (MIS-C). Incidence of MIS-C is two per 100,000 compared with 322 per 100,000 children's with COVID 19 infection.[1] MIS-C present with persistent fever, rash, gastrointestinal symptoms, myocardial dysfunction, vasoplegic or cardiogenic shock, and cytokine storm.[2] These features resemble various other conditions like Sepsis, Kawasaki disease, Hemophagocytic Lymphohistiocytosis and Macrophage activation syndrome. Majority of these children (70-80%) have myocardial dysfunction and some develops coronary dilatation.[3]

Children with MIS-C display increased macrophage activation and hyperphagocytosis with cytokine storm, Helper T-cell activation, and inflammation stimulated by antibodies and expansion of immunoglobulin.[4-6] Most of these children are RT-PCR negative and SARS-CoV-2 antibody positive, suggesting immune mechanism behind this. As cases of MIS-C have increased in children, better understanding of this life threatening illness is required.

In this study, we found out various demographic features of children with MIS-C. We also evaluated common clinical presentation, clinical and laboratory markers of severity, and outcome of children admitted with MIS-C.

METHODS

This study is a prospective observational study conducted on children with MIS-C admitted to Department of Pediatrics of Nobel Medical College and Teaching Hospital during 12 months period from July 2021 to June 2022. This study was started after acquiring approval from the Institutional Review Committee of Nobel Medical College (IRC). Nobel Medical College is a tertiary referral center located in Biratnagar, Nepal. Department of Pediatrics consists of 63 bedded pediatric ward and 15 bedded level III pediatric intensive care unit.

Primary objective of this study was to describe demographic features of children with MIS-C. Secondary objectives were clinical presentation, clinical and laboratory markers of severity in MIS-C and Outcome (Duration of Hospital/PICU stay, need of vasoactive agents, and development of myocardial dysfunction or coronary aneurysm, mortality) in children admitted with MIS-C. All children who were one months to 19 years of age fulfilling criteria of MIS-C according to WHO criteria (Table 1) were enrolled in this study with a temporal association with confirmed or probable COVID 19.[7] Children fulfilling the clinical criteria of MIS-C, with definite infective etiology other than COVID 19 were excluded from the study (Blood culture positivity, Serological tests for endemic infectious disease, prevalent in our region).

Table 1. Showing WHO case definition of MIS-C

WHO CASE DEFINITION[7]
All 6 criteria must be met:
1. Age 0 to 19 years
2. Fever for ≥ 3 days
3. Clinical signs of multisystem involvement (at least 2 of the following):
Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet)
Hypotension or shock
Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP)
Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer)
Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes
6. Evidence of SARS-CoV-2 infection
Any of the following: Positive SARS-CoV-2 RT-PCR Positive serology Positive antigen test Contact with an individual with COVID-19

Infective causes like Enteric fever, Dengue, Malaria, Leptospirosis, Scrub typhus and bacterial sepsis were excluded by appropriate investigations. COVID 19 RT PCR and COVID 19 antibody testing was done in all suspected cases fulfilling MIS-C criteria. After consent from caregiver and assent from older children, Basic demographic features, presence of any chronic illness, nutritional status, and data on significant family illness and social and economic factors were noted. Presenting complaints and contact history of COVID 19 infection was documented. Electrocardiogram, chest X-ray and Bedside echocardiography were done in all patients with MIS-C with shock at admission. All patients were seen by cardiologist to look for coronary artery status. Z-score of coronary artery diameter > 2 was considered to have coronary artery aneurysm.[8] Sequential organ failure score (SOFA) was used to define multiorgan dysfunction. Shock was defined when a patient required more than 20 ml/kg of IV fluid resuscitation or inotropic support to maintain blood pressure above the 5th centile. Other variables were collected like inflammatory markers, duration of hospital/PICU stay, need for inotropic support, duration of shock, type of respiratory support required, coronary artery changes at admission and 2 to 6 weeks follow-up and mortality.

Data was entered in MS Excel and analyzed using SPSS 20. Data was summarized using mean and standard deviation for quantitative variables and frequency and percentage for qualitative variables. Independent sample t-test was used for comparison of means. Categorical variables between groups were compared using chi square test. Logistic regression was done to assess the relationship between

clinical variables and outcome. Results were considered significant if p value < 0.05. In various studies, the incidence of MIS-C in children with SARS-CoV-2 infection has been reported to be 0.14-0.62%.[1,9] We calculated sample size of 10, using sample size formula [$N=Z^2pq/d^2$ (where q = 1-p)] and incidence of 0.62%.[9] However, we included all the cases being admitted as MIS-C during the study period and consenting to participate in this study. Sample size formula:

$N=Z^2pq/d^2$ (where q = 1-p) where,

Z=1.96 (value of standard normal distribution corresponding to a significance level of 0.05)

d=Error of margin (0.05)

p=Expected prevalence

RESULTS

A total of 36 children were included in our study. Among them, 22 were male (61.11%) and 14 (38.88%) were female. We found five (13.88%) cases between 1-5 years of age, 10 (27.77%) cases between 5-10 years of age and 21 (58.33%) cases were above 10 years of age. Mean age of patients was 11.2 years. Fever was found in all (100%) cases, 69.4% had abdominal symptoms, 66.6% had respiratory distress, 50% had hypotension at time of admission, 16.6% had neurological involvement in form of encephalopathy or seizure, and 36.11% had rash or muco-cutaneous involvement (Table 2).

Table 2. Showing clinical features of children with MIS-C

Symptoms	Number (%)
Gastrointestinal Symptoms	25 (69.4%)
Mucocutaneous Involvement	13 (36.11%)
Rash	11 (30.55%)
Lymphadenopathy	4 (11.11%)
Edema	6 (16.66%)
Shock	18 (50%)
Severe LV Dysfunction	9 (25%)
Myocarditis	4 (11.1%)
Coronary Artery Involvement	3 (8.3%)
Acute Kidney Injury (AKI)	11 (30.55%)
Respiratory Distress	24 (66.6%)
Acute Respiratory Failure	8 (22.2%)
Neurological Involvement	6 (16.6%)
MODS (Multiple Organ Dysfunction Syndrome)	10 (27.7%)

Laboratory parameters showed leukocytosis in 95% of cases, 68% cases showed lymphocytopenia and 52% cases showed thrombocytopenia. Mean CRP level was 96 ± 44 mg/l, and Erythrocyte sedimentation rate was 5 ± 36 mm in the first hour. Transaminases were raised in 78%, deranged coagulation profile in 38%, hypoalbuminemia in 82%, 31% had hyponatremia and 71% had hyperferritenemia. Serum LDH was elevated in 48% cases, 36% had high triglycerides, 43% had elevated D-Dimer and18% had elevated troponin and Pro-BNP. Children requiring mechanical ventilation had significantly higher CRP [92 (22.6) vs 48 (36.1) mg/l; p value 0.0026], lower platelets [18,600 (11,200) vs 55,400 (19,300)/cu mm; p value < 0.0001], higher D-Dimer [5.9 (3.2) vs 3.8 (1.9) mcg/ml; p value 0.0248] and lower ejection fraction [45 (13) vs 60 (12) %; p value 0.0043]. Out of 36 children, 31 were antibody positive, three were COVID PCR positive, and two were both antibody and PCR negative but were epidemiologically related to COVID 19 cases.

Among 36 children, 28 (77.77%) children required Intensive care treatment. Oxygen via nasal cannula was required in 12 (33.33%) children, four (11.11%) children required CPAP support, four (11.11%) children required oxygen via High flow nasal cannula and eight (22.22%) children required mechanical ventilator support. Out of 36 children, 18 (50%) had features of shock, only six (33.3%) out of 18 children were fluid responsive, 12 (66.6%) were fluid resistant and required ino-vasopressor earlier after admission. Vasoactive Inotropic score (VIS score) > 10 was associated with higher chances of mechanical ventilation [87.5% vs 12.5%, p value 0.0037] and longer duration of Pediatric intensive care unit stay [9.5 (2.8) days vs 5.5 (1.8) days, p value < 0.0001]. All of them were treated with broad spectrum antibiotics at presentation and antibiotics were deescalated after culture reports.

Out of 36 children, 13 (36.11%) children received only Methyl prednisolone @ 2 mg/kg/day due to mild illness, nine (25%) children with severe LV dysfunction received Pulse Methyl prednisolone 10-30 mg/kg/day for 3 days, followed by slow tapering, and 14 (38.88%) children received both IVIG and Methyl prednisolone. All children received low dose aspirin 3-5 mg/kg/day if platelets > 80,000 until normalization of platelet count and confirmed normal coronaries at 4-6 weeks after diagnosis and 12 (33.33%) children received Enoxaparin 1 mg/kg/dose every 12 hourly during hospital stay, if they had coronary aneurysm and severe LV dysfunction. Three (8.3%) children developed coronary aneurysm; all of them were treated with both IVIG and Methyl prednisolone. On three month follow up, all three coronary aneurysm resolved and children who survived, had normal LV function. Children with MIS-C had good prognosis, 33 (91.6%) children with MIS-C were discharged, 2 (5.55%) of them expired and 1 went on LAMA owing to poor prognosis. Two children, who expired, had refractory shock and severe LV dysfunction. Mean duration of PICU stay was 7.5 days.

DISCUSSION

We studied 36 children with MIS-C, among whom 28(77.77%) required PICU admission and eight (22.22%) children required mechanical ventilation. In our study, common age of presentation was > 10 years (58.33%) and had male predominance (61.11%), similar to study done by

Ramcharan et al. where median age of presentation was 8.8 years.[10] Adolescent male are more prone for Covid infection, making them more favorable age group for MIS-C. In our study, we found out gastrointestinal symptoms (69.4%) were more common, followed by respiratory (66.6%) and cardiovascular (50%). Other systemic findings were less common, renal (30.55%), mucocutaneous (36.11%) and neurological symptoms (16.6%) similar to study done by Radia et al.[11] Similar to the respiratory tract, SARS-CoV-2 binds to GI tract cells via the ACE-2 and TMPRSS2 cell receptors in the intestine causing release of cytokines. In children these ACE-2 receptors are more prevalent in GI tract as compared to respiratory tract, resulting in more severe gastrointestinal symptoms. Early detection of MIS-C and early management of shock might have resulted in lesser renal and neurological involvement.

Laboratory parameters showed leukocytosis in 95% of cases, 68% cases showed lymphocytopenia and 52% cases showed thrombocytopenia, similar to study done by Radia et al.[11] Systemic review conducted by Hoste et al. also reported association of MIS-C with high inflammatory markers.[12] Besides high inflammatory markers, coagulation markers were also substantially upregulated and markers of myocardial injury were also often elevated. Mean CRP level in our study was 96 ± 44 mg/l, and ESR 55 ± 36 mm in the first hour, lesser than study done by Whittaker et al., where mean CRP level was 229 mg/l.[13] In this study done by Whittaker et al. higher CRP, neutrophil count, lower albumin, lower lymphocyte count, and elevated troponin, was associated with higher incidence of shock and coronary artery dilatation.[13] This result is similar to our findings, where high CRP, low platelets, high D-Dimer and low ejection fraction was associated with more severe course of disease and requiring mechanical ventilation. Higher inflammatory markers are associated with more severe systemic inflammation, which results in coronary artery involvement.

Covid IgG antibody was positive in 31 cases (86.11%), which is similar to study done by Whittaker et al. where 87% of children were covid IgG positive. Covid PCR was positive only in three cases (8.33%) in our study, which is lower (25%) as compared to study done by Whittaker et al. MIS-C is a delayed hyperinflammatory syndrome, which might have resulted in low covid PCR positivity rate.[13] Occasionally covid PCR can be positive for long period due to detection of dead virus as well. Among 36 children, 77.77% children required Intensive care treatment. Among them, 16 (44.44) required respiratory support, whereas eight (22.22) required invasive mechanical ventilation. Eighteen (50) children had features of shock, only six (33.3) out of 18 children were fluid responsive, 12 (66.6) required ino-vasopressor earlier after admission. Severe LV dysfunction was seen in nine (25%) cases. These findings were similar to study done by Sethy et al. where among 21 children with MIS-C, 48% presented in shock and 38.1% children had myocardial dysfunction.[14] VIS score > 10 was associated with higher chances of mechanical ventilation [87.5% vs 12.5%, p value 0.0037] and longer duration of PICU stay [9.5 (2.8) days vs 5.5 (1.8) days, p value < 0.0001]. Higher requirement of vasoactive substance, suggest more severe form of disease and more severe myocardial dysfunction, which explains increased need of mechanical ventilation and prolonged PICU stay.

Intravenous Immunoglobulin, steroids, anticoagulation and aspirin are mainstay of therapy in management of MIS-C but various studies has used different protocol. In our study out of 36 children, 13 (36.11%) children received only Methyl prednisolone, nine (25%) children with severe LV dysfunction received Pulse Methyl prednisolone and 14 (38.88%) children received both IVIG and Methyl prednisolone. The decision of IVIG or steroid or both was taken based on clinical presentation, severity at presentation and presence of LV dysfunction. Because of financial issues, few patients were treated with steroid in place of IVIG, however they all improved. Many clinical trials have suggested use of IVIG with or without steroids for management of MIS-C. Whittaker et al. reported 100% use of IVIG for Kawasaki like presentations, 72% for those with shock, and 61% for those with febrile inflammatory state.[13] Three (8.3%) children developed coronary aneurysm in our study. On three month follow up, all three coronary aneurysm resolved. In a recent study from India, coronary involvement was found in 23.8%.[15] Higher rate of coronary involvement could be due to use of IVIG in only 50% of cases. Mortality in our study is 5.55%, which is comparable to studies from western literature (1.8-3%).[1] All of them had refractory shock and severe LV dysfunction.

It's a single center study, limiting its wide validity. As its single center study, sample size of study was small owing to rare complication of COVID 19 infection. To increase the sample size, we collected all MIS-C cases being admitted during the study period. Problems of confounders and selection bias, was bound to happen as it is observational study.

CONCLUSION

MIS-C is life threatening illness in children following COVID 19 infection. Diagnosis and management of MIS-C requires early suspicion and appropriate intervention to prevent mortality. Results of this study would be helpful in knowing demographic features, associated risk factors, and predictors of severity and outcome of the condition. This knowledge would be of help for formulation of hospital based specific guideline and in future might be helpful in formulating national guidelines.

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