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Clinical profile and outcome of multisystem inflammatory syndrome in children (MIS-C) related to COVID-19 infection: A single center retrospective study

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Abstract: Background and Objectives: Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 is a hyper inflammatory syndrome manifesting commonly with a cytokine storm that causes wide spread multi organ involvement.
Aim: To study the clinical profile & outcome of multisystem inflammatory syndrome in children (MIS-C) related to covid-19 infection.
Methodology: This retrospective study was done in Pediatric Intensive Care Unit of a tertiary care teaching hospital. Case records of children with discharge diagnosis of MIS-C, full filling the WHO criteria were included. The cases were categorized into two subsets based on presentation: with shock and without shock. Demographic parameters, clinical symptomatology, laboratory parameters, echocardiography findings and treatment were compared between these two groups. Coronary artery diameter was measured by using Z score in echocardiography. Outcome of the study was measured in terms of mortality or discharged.
Results: During the study period, 96 children presented with signs and symptoms suggestive of MIS-C and out of them 63 children fulfilled the WHO MIS-C criteria. The mean age of study population was 6.8 ± 5.31years (1 month-17 years). Majority of cases were in the age group of 0-5 years (47.61%) with male preponderance of 55.55%. Half (50.79%) of the children presented with shock and maximum cases were in 6-12 years of age group (p=0.008). Most common presenting symptoms were vomiting and rash observed in 58.73% children each. C reactive protein (p=0.001) and Sr Ferritin (p=0.009) were significantly higher in children with shock. Echocardiography was done in 38 children and 30(78.94%) of them had abnormalities. Left ventricular dysfunction was significantly higher in children with shock as compared to those without shock (p=0.02). Majority of children who presented with shock required IVIg along with steroids as against those presented without shock(p=0.003). Mortality was 12.7%.
Conclusion: Shock was a common manifestation in MISC, affecting half of the children. CRP, Sr ferritin and echocardiography abnormality were significantly higher in children with shock. Majority of the children with shock required IVIg along with steroids.

Keywords: Multisystem inflammatory syndrome in children (MIS-C); Pediatric Intensive Care Unit (PICU); Shock; LV dysfunction.

1. Introduction

A new corona virus that spread quickly to a pandemic level was identified in late 2019. The severe acute respiratory syndrome coronavirus 2 virus, which causes COVID-19. In April 2020, reports from the United Kingdom described a child presentation resembling incomplete Kawasaki disease or toxic shock syndrome. Since then, reports of children in other regions of the world who were similarly impacted have appeared [1,2]. Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, also known as pediatric inflammatory multisystem syndrome temporarily associated with SARS-COV-2 (PIMS-TS), is a hyper-inflammatory syndrome that develops in conjunction with severe acute respiratory syndrome corona-virus 2 infections in children and is frequently characterized by a cytokine storm that results in widespread multi-organ involvement [3]. Uncertainty surrounds the pathophysiology of MIS-C.

It is understood that SARS-COV-2 enters cells via attaching to the highly expressed ACE-2 protein found in cardiac myocytes, alveolar cells, vascular endothelium, and a small proportion of immune cells [4]. Evidence suggests that multi-organ failure in severe COVID-19 and MIS-C may be caused by a dysregulated innate immune response that causes a cytokine storm and endothelial damage. The features of MIS-C include fever, gastrointestinal symptoms, rash, conjunctivitis, cardiac and renal dysfunction, shock and coagulopathy severe enough to require treatment in the intensive care unit [1]. Toxic shock syndrome, macrophage activation syndrome (MAS), hemophagocytic lymphohistocytosis (HLH), and typical/atypical Kawasaki disease are all included in the MIS-C spectrum. The mucocutaneous, gastrointestinal, cardiovascular, or neurological systems are also frequently affected. Unlike typical Kawasaki disease, most children with MIS-C present with shock and need ionotropic support [2]. Children were not particularly vulnerable to severe COVID-19 symptoms, such as severe acute respiratory syndrome (SARS), at the start of the pandemic. As the pandemic progressed, the pediatric age group with MIS-C experienced progressively severe complications, such as thrombotic events, myocardial dysfunction, and coronary artery disease.

2. Material and Methodology

This retrospective study was done in Pediatric Intensive Care Unit of tertiary care teaching hospital. Case records of children in the age group of 1 month to 18 years with discharge diagnosis of MIS-C admitted to Paediatric Intensive Care Unit from June 2020 to December 2022(30 months), full filling the WHO criteria were included in study. Data was filled on preformed structured proforma. The study protocol was approved by institutional ethical committee. The cases were categorized into two subsets based on presentation: with shock and without shock. Demographic parameters, clinical symptomatology, laboratory parameters, echocardiography findings and treatment were compared between these two groups. Coronary artery diameter was measured by using Z score in echocardiography. Outcome of the study was measured in term of mortality or discharged. Children with discharge diagnosis of MIS-C with incomplete record were excluded from study. WHO case definition of MIS-C [5].

2.1. Statistical analysis

The data was collected on data sheet and appropriate parametric and non-parametric tests were used. Data was analyzed using statistical software SPSS version 20.0. Various statistical measures such as descriptive statistical analysis like frequency, percentage, mean and standard deviation was calculated and appropriate statistical methods like Chi square test, t test was applied on the data.

2.2. Ethical approval

This study protocol was approved by The Chairman, Institutional Ethics Committee Bharati Vidyapeeth (Deemed to be University) Medical college and hospital Sangli Maharashtra BV(DU)MC&H/Sangli/IEC/499/22.

3. Results

During the study period of 30 months (June 2020 to December 2022), 96 children presented with signs and symptoms suggestive of MIS-C. Out of them 63 children who fulfilled the WHO MIS-C criteria were included in study. Temporal distribution of cases showed 23 cases within 6 months of the first wave in 2020, 23 cases and 17 cases each in 2021 and 2022 respectively. The mean age of study population was 6.8 $\pm$ 5.31 (1 month - 17 years) years and mean duration of fever was 4.76 $\pm$ 2.41days. Half (50.79%) of the children presented with shock. Vomiting and rash were the most common presenting symptoms observed in 58.73% children each followed by diarrhea and abdominal pain in 38.09% and 36.50% children respectively. KD like presentation was seen in 5 children (7.93%). Comparison of presenting manifestations in different age groups are shown in Table 1. Abdominal pain (p=0.008), conjunctivitis (p=0.03) and shock (p=0.008) were more common in the age group of 6-12 years, whereas convulsions were seen mainly in the age group of 1-5 years (p=0.01).

On comparing the groups with and without shock there was no significant difference in the clinical parameters except that shock was more common in females (p=0.01) (Table 2). C reactive protein (p=0.001) and Sr Ferritin (p=0.009) were significantly higher in children with shock (p<0.05). (Table 3). Mean PICU stay in shock was 5.63 $\pm$ 3.02 days and 4.86 $\pm$ 3.88 days in non- shock group.

Echocardiography was done in 38 children and 30(78.94%) of them had abnormalities. Nine children with shock did not have echocardiography as they promptly responded to fluid therapy. Echocardiographic abnormalities were significantly high in the shock group ($p<0.05$). LV dysfunction was higher in children with shock as compared to those without shock. ($p=0.02$). Children with KD like presentation had coronary dilatation with no LV dysfunction on echocardiography (Table 4).

Use of combination therapy with IVIg and steroid was significantly higher in the shock group ($p=0.003$). Steroids alone was the mainstay of treatment in the non- shock ($p=0.003$) (Table 5). Five children (7.96%) presented with mild variety of MIS-C and did not require steroid or IVIg. Pneumonia, acute respiratory distress syndrome and coagulopathy like complications were observed in 22.2%, 3.17% and 9.52% children respectively. The mean length of PICU stay was 5.27 ± 3.44 days. Mortality was12.7% (8/63). Causes of death included ARDS (25%), refractory shock (50%) and severe LV dysfunction (25%).

Table 1. Comparison of presenting manifestations in different age group

	1-5 years (n-30)	6-12 years (n-20)	13-18 years (n-13)	P value
Vomiting	15 (50%)	14 (70%)	8 (61.53%)	0.36
Abdominal pain	10 (33.33%)	12 (60%)	1 (7.69%)	0.008
Diarrhoea	14 (46.66%)	6 (30%)	4 (30.76%)	0.41
Rash	16 (53.3%)	14 (70%)	7 (53.84%)	0.46
Conjunctivitis	2 (6.6%)	7 (35%)	2 (15.38%)	0.03
Oral cavity changes	2(6.66%)	3(15%)	0(0%)	0.28
Shock	16 (53.33%)	14(70%)	2(15.38%)	0.008
Cough	12 (40%)	2 (10%)	4 (30.76%)	0.06
Breathlessness	7 (23.33%)	7 (35%)	4 (30.76%)	0.66
Convulsions	11 (36.66%)	1 (5%)	1 (7.69%)	0.01

Table 2. Distribution according to General characteristics

Characteristics	Number (n-63)	With shock (n-32)	Without shock (n-31)	P value
Age at presentation (Years) *	6.80±5.31	5.54±4.32	8.09±5.97	0.05
Male	35(55.55%)	13	22	0.01
Female	28(44.48%)	19	9	
Duration of fever (Days) *	4.76±2.41	4.69±2.00	4.84±2.79	0.81
Duration of PICU stay (Days) *	5.27±3.44	5.63±3.02	4.86±3.88	0.38
Fever	63(100%)	23	23	0.84
Respiratory symptoms	19(30.15%)	8	11	0.53
Neurological-Symptoms	24(38.09%)	14	10	0.50
Gastrointestinal symptoms	51(80.95%)	27	24	0.70
Mucocutaneous	40(63.49%)	22	18	0.54
Cardiovascular symptoms	18(28.57%)	11	7	0.45
Positive family history	9(14.28%)	4	5	0.96

* Mean ± standard deviation

Table 3. Distribution according to Laboratory Parameters

Laboratory Parameters #				
	Total (n-63)	With shock (n-32)	Without shock (n-31)	P value
Hb	10.5(9.5-11.6)	1035(9.63-11.45)	10.7(9.5-11.7)	0.79
TLC	15800(9400-21700)	16480(9850-21975)	13300(9300-21700)	0.57
Platelets	365000(275000-586000)	401500(284500-574500)	357000(264000-647000)	0.97
ESR	24.5(18.5-32)	24.5(21.3-35.25)	25(13.5-34)	0.67
Blood Urea	29(19-39)	28(20.25-38)	30(19-39)	0.98
Sr. Creatinine	0.7(0.6-0.9)	0.7(0.63-0.9)	0.7(0.6-0.8)	0.95
SGOT	58(28-130)	48(27-107.75)	60(29-151)	0.71
SGPT	36(15-76)	35(16.75-74)	36(14-109)	0.97
PT	16.25(14.33-19.4)	16.75(15.3-19.5)	16(14.05-19.35)	0.37
APTT	36.75(33.2-41.68)	37.2(32.6-43.2)	36.3(33.45-41.05)	0.84
INR	1.3(1.2-1.6)	1.3(1.23-1.7)	1.3(1.2-1.55)	0.54
Q CRP	89.05(64.75-133)	116.25(80.25-168.75)	72.45(26.25-98.25)	0.001
Ferritin	343(108-1100)	830(170-1580)	274(89.75-476.75)	0.009
LDH	816(563.5-1264)	749.5(552.25-1091.8)	868(566-1466)	0.4
IL6	122(13.7-853)	146(13.7-990)	118(16.7-538)	0.8
CPK total	140(78-353)	158(84-514.5)	115(74-253.5)	0.32
CPK MB	31(20-48)	29.5(21.75-51)	31(20-47)	0.83

Median (IQR)

Table 4. Distribution according to echocardiography findings

Echocardiography findings	Total (n-38)	With shock (n-23)	Without shock (n-15)	P value
Coronary dilatation	6 (15.78%)	1 (4.37%)	5 (33.33%)	0.01
LV dysfunction	19 (50%)	15 (65.21%)	4 (26.66%)	0.02
Both	5 (13.15%)	5 (21.73%)	0 (0%)	0.05

Table 5. Distribution according to treatment modality

Treatment modality	Total No(n-63)	Percentage (%)	With shock (n-32)	Without shock (n-31)	P value
Steroids	34	53.96%	11	23	0.003
IVIg	4	6.34%	4	0	0.13
Steroids + IVIg	20	31.74%	16	4	0.003
Anticoagulation (LMWH)	31	49.20%	15	16	0.90
Mechanical ventilation	13	20.63%	10	3	0.07

4. Discussion

The present retrospective study was done in a tertiary care hospital. Total of 96 children presented with the signs and symptoms suggestive of MIS-C during the study period of 30 months (June 2020 to December 2022). In India, the first wave began in March 2020 and lasted till nearly December 2020, while second wave began in March 2021 lasting till the end of June 2021. In April 2020, the first MIS-C reports came from the United Kingdom. Since then, reports of children in other regions of the world who were similarly impacted have appeared [1,2]. Notably, early in the pandemic there were disproportionately few reports of MIS-C from China and other Asian countries with high COVID-19 rates. The duration between an active COVID 19 infection and onset of symptoms of MISC is reported to be around 4 to 6 weeks. We observed that cases of MIS-C started presenting after 2 months from the first pandemic. Temporal distribution of cases showed 23 cases within 6 months of the first wave in 2020, 23 cases and 17 cases each in 2021 and 2022 respectively.

MIS-C mimics are certain other conditions which have similar presentation like MIS-C, these include Kawasaki disease, bacterial sepsis, Toxic shock syndrome and tropical febrile illness (Leptospirosis, scrub typhus, dengue etc.) [6]. With MIS-C and KD, there is some phenotypic overlap. While KD mainly

affects young children, MIS-C commonly affects older children. Gastrointestinal symptoms, shock and myocardial dysfunction are more common in MIS-C. Mucocutaneous symptoms and coronary dilatation are more common in KD [7,8]. In tropical countries due care should be taken to exclude alternative mimicking condition before making a diagnosis of MIS-C.

In our study the mean age of the study population was 6.8 $\pm$ 5.31years (1 month-17 years), with male preponderance (55.55%) and 47.61% of children presenting with MIS-C were < 5 years which was similar to study by Gupta et al and Balagurunathan M et al [9,10]. Mean duration of fever was 4.76 $\pm$ 2.41days. Half (50.79%) of the children presented with shock and maximum cases were in 6-12 years of age group (p=0.008), which was comparable with previous report [3,4]. Vomiting and rash were the most common presenting symptoms observed in 58.73% children each followed by diarrhea and abdominal pain in 38.09% and 36.50% children respectively, which was similar with previous reports [4,6]. KD like presentation was reported in 5 children (7.93%) in our study. In study by Nayak S et al, KD like features were seen in 9 (6.7%) children and majority of them were in 6-12 years [11]. Abdominal pain, conjunctivitis and shock were more common in the age group of 6-12 years, whereas convulsions were seen mainly in the age group of 1-5 years, which was similar to studies by Tiwari A et al and Sai BVK et al [4,12].

In the study we attempted to compare the clinical, laboratory and echocardiographic findings in children presented with and without shock. Presentation with shock was significantly higher in female children (p=0.01), which was similar to an earlier study [3]. CRP and Sr Ferritin were significantly higher in children with shock (p<0.05), which is in accordance with studies by Jain S et al and Balagurunathan M et al [3,10]. Cardiac markers like troponin T and NT-proBNP were not done in all patients, thus not included in study. Procalcitonin was done in 13 children and was raised in all of them. Cardiac assessment with an echocardiography was done in 38 children among which LV dysfunction was observed in 19 (50%), dilated coronaries in 6(15.78%) and both were observed in 5 (13.15%) children. LV dysfunction was higher in children with shock as compared to those without shock (p=0.02). Notably all children with KD like presentation had dilated coronaries with normal LV function on echocardiography. Similar results of LV dysfunction and coronary dilatation were observed previous studies [3,4].

Due to striking similarity of MIS-C with Kawasaki disease, the same treatment is being recommended [12]. In our study it was observed that majority of the children who presented with shock required IVIg along with steroids (p=0.003). In most of the studies commonly used therapy in MIS-C patient is IVIg along with high dose steroids [9,11,13,14]. Steroids alone was the mainstay of treatment in the children presented without shock. Initial treatment with IVIg plus steroids reduced the incidence of new or enduring cardiovascular dysfunction among children with MIS-C compared to IVIg alone. Mean PICU stay in shock was 5.63 $\pm$ 3.02 days and 4.86 $\pm$ 3.88 days in non- shock group. Thirteen children (20.63%) required mechanical ventilation, which was comparable with previous report [4].

Mortality in our study was 12.70% (8 cases). Our findings are similar to other Indian studies [11,15] acute respiratory distress syndrome, severe LV dysfunction and shock were the most common causes of death.

5. Conclusion

Shock was a common manifestation in MISC affecting half of the children. CRP, Sr ferritin and echocardiography abnormality were significantly higher in children with shock. Majority of the children with shock required IVIg along with steroids.

6. Limitations

Our study is retrospective in nature and hence bound to biases. Echocardiography was not done in all patients and it's possible that mild abnormalities might have been missed. We have not included procalcitonin and cardiac markers as they were not done in all cases. Being a single center experience our findings may not be generalizable.

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