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Original Paper

Unusual Clinical Manifestations and Outcome of Multisystem Inflammatory Syndrome in Children (MIS-C) in a Tertiary Care Hospital of North India

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ABSTRACT

Till date, there is paucity of published literature on clinical manifestations of Coronavirus disease 2019 (COVID-19) in children from low-middle-income countries (LMIC). Most of the reports are from Europe, USA or China. Our study aimed to capture data on varied and unusual clinical presentation and management of MIS-C (Multisystem Inflammatory Syndrome in Children) with COVID-19 and compare the MIS-C and non-MIS-C children. This was a single-centre cohort study of 41 COVID positive children 0–12 years age hospitalized between 1 April 2020 and 31 July 2020. Data were entered into standardized WHO Case Report Form and analysed using strata 15.0 statistical software. Twenty out of 41 children fulfilled the criteria of MIS-C. Male-to-female ratio in the cohort was 1.73:1. In MIS-C cases, predominant clinical manifestation was fever (100%), neurological manifestations (80%), lower respiratory tract infection (50%), rash (35%) and acute gastroenteritis (25%). They were categorized into Acute Encephalitis-like illness in 35%, Kawasaki-like disease, Toxic Shock-like syndrome and Comorbidity with systemic complications in 20% each. Ninety percent of MIS-C cases required oxygen supplementation with odds ratio (OR) 18 (3.22–100.48), whereas 65% required mechanical ventilation with OR 37.14 (4.08–338.10). Most of them had raised inflammatory markers and hepatic enzymes derangement. Steroids, Intravenous immunoglobulin and supportive therapy were mainstay of management for MIS-C group. Most MIS-C group children had multisystem involvement with predominant neurological manifestations at time of presentation. Delay in diagnosis and referral may have adversely affected the prognosis and outcome.

KEYWORDS: MIS-C, Kawasaki disease, toxic shock syndrome, SARS-CoV2

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2), a novel coronavirus was first notified in Wuhan, China by World Health Organization (WHO) in December 2019. Over next 3 months the Coronavirus disease 2019 (COVID-19) was declared a pandemic [1]. In adults, COVID-19 causes severe lung involvement with acute respiratory failure and multiorgan failure, typically seen during second week of illness when viral titres are declining and markers of inflammation are rising, labelled as cytokine storm [2–4]. Initial reports from COVID-19 pandemic hinted that children were less severely affected by SARS-CoV2 infection than adults [5, 6]. A retrospective study of 2135 children from China reported 5.8% severe and critical illness in children [6].

National Health Services, UK reported a severe Kawasaki disease (KD)-like syndrome in children and termed it as Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV2 [7]. A similar presentation of KD-like illness was reported in paediatric population from Bergamo Province, Italy which reported an increased monthly incidence of KD in a cohort of children during this pandemic when compared with a cohort of patients from previous 5 years [8]. Multisystem Inflammatory Syndrome in Children (MIS-C) was described by Centres for Disease Control (CDC) as severe illness associated with COVID-19 in children requiring hospitalization [9].

According to available literature till now, the spectrum of MIS-C is a combination of typical/atypical KD, toxic shock syndrome(TSS) and macrophage activation syndrome(MAS)/hemophagocytic lymphohistiocytosis (HLH) with prominent involvement of mucocutaneous, gastrointestinal, cardiovascular or neurological systems. Majority of children with MIS-C, unlike typical KD presented with shock requiring ionotropic support [10]. Few reports described a presentation similar to that of toxic shock syndrome and secondary MAS/HLH [8, 10]. A study of 44 children from Columbia, USA has described gastrointestinal symptoms in 84% of patients meeting MIS-C criteria. KD-like features were present in 50% of patients. They also reported neurological manifestations in 30% [11]. Another study from Asia, India has shown KD-like presentation in 36% and gastrointestinal presentation in 42%. Neurological manifestations were seen in 31% of patients with MIS-C [12].

There is paucity of data on MIS-C from Asian continent especially lower middle-income countries. None of the larger studies or meta-analysis has reported neurological manifestations or Encephalitis-like syndrome. Although single centre but some recent studies have talked about the neurological and cardiac manifestations of MIS-C. Also, only few have compared the clinical and biological features of MIS-C with other presentations of SARS-CoV2. With this background, we planned a study of COVID-19 positive children admitted to our hospital between 1 April and 31 July 2020. We documented the clinical profile of all COVID-19 positive children and compared the demographic, clinical and laboratory characters of MIS-C with non-MIS-C children.

METHODOLOGY

Study design and participants

It is a retrospective cohort study consisting of all 41 children screened positive for SARS-COVID-19 and admitted to our hospital between 1 April and 31 July 2020. The hospital is a 2800 bedded referral tertiary care public hospital of North India. The hospital receives referrals and sick and critical patients from many satellite centres of Delhi and from Northern states. The Institutional Ethical clearance was obtained to conduct the study. All the childre/n had recent or past infection of SARS-CoV2 confirmed by reverse transcriptase polymerase chain reaction(RT-PCR) and/or immunoglobulin G to SARS-COVID-19, categorized into MIS-C and non-MIS-C using the CDC case definition [9].

Case definitions

MIS-C:

i. Presence of fever: An individual aged <21 years presenting with fever*, laboratory evidence of inflammation** and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic or neurological); AND

ii. No alternative plausible diagnoses; AND
iii. Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. (*Fever ≥38.0°C for ≥24 h, or report of subjective fever lasting ≥24 h).

Confirmed case: It is defined as a patient in whom COVID-19 infection was detected by RTPCR or immunoglobulin assay.

Duration of illness: onset of symptoms till outcome (death/discharge)

Outcome: Death or discharge from hospital.

Fever is defined as body temperature of at least >38*C for more than 24 h.

Diagnosis of upper/lower respiratory tract infection was made on basis of clinical presentation and chest X-ray (CXR) findings.

Ionotropic support was defined as administration of drugs like Dopamine, dobutamine and adrenalin.

KD as illness in a patient with fever of 5 or more days duration (or fever until the date of administration of intravenous immunoglobulin (IVIG) if it is given before the fifth day of fever), and the presence of at least four of the following five clinical signs: rash, cervical lymphadenopathy (at least 1.5 cm in diameter), bilateral conjunctival injection, oral mucosal changes and peripheral extremity changes [13].

In incomplete types (fever for ≥5 days plus two or three of the aforementioned clinical criteria), the values of erythrocyte sedimentation rate or C-reactive protein (CRP) or both, were taken as an additional diagnostic criterion in association with the presence of anaemia, thrombocytosis after 7 days of fever, hypoalbuminemia, hypertransaminasemia, leucocytosis, sterile pyuria or an echocardiogram showing coronary aneurysms or cardiac dysfunction [13].

Data collection

Data were abstracted from medical case records into standardized Case Report Form of WHO Global COVID-19 Clinical Platform. Data included demographic profile, history of contact with COVID positive patient, any pre-existing medical illness, various variables of clinical presentation and the management of cases during hospitalization. Relevant data were captured on investigations complete blood count, serum electrolytes, liver enzymes, inflammatory markers like CRP, serum ferritin, interleukin-6 (IL-6), D-dimer, coagulation profile, creatine phosphokinase-MB (CPK-MB), procalcitonin and CXR. Outcome of the study was measured in terms of mortality and cases requiring respiratory support.

Statistical analysis

Data were recorded on a pre-designed proforma and managed on an Excel spreadsheet. Categorical variables were expressed as frequency (%). Chi-square test was used to assess association of categorical variables between MIS-C and non-MIS-C and their outcomes. Bivariate logistic regression was used to estimate odds ratio (OR) with 95% CIs. Stata 15.0 statistical software was used for data analysis. In this study, p value < 0.05 is considered as statistically significant.

RESULTS

During study period, 41 patients of age 0–12 years old presented with signs and symptoms suggestive of SARS-COVID-19 infection. Forty children were confirmed with only RTPCR (serology not done), whereas one child had Immunoglobulin G positive for SARS-CoV-2. The male to female ratio in the cohort was 1.73:1. History of contact with a SARS-COVID positive patient in family was present in 24.3% of cases. Fifty-one percent of the children in the cohort had a history of coexisting illness. Mean duration of illness in the cohort was 10 days. Twenty out of 41 children fulfilled the criteria of MIS-C. The demographic and clinical profile of the cohort were compared between MIS-C and non-MIS-C groups (Table 1).

Clinical features of MIS-C

Fever was presenting feature in 75% of total cases. Forty-three percent of COVID positive children presented with acute febrile illness with lower respiratory tract infection (LRTI). All 20 cases of MIS-C had fever (>38°C) at presentation. Most common

Table 1. Demographic and clinical profile of COVID positive children (MIS-C & non-MIS-C)

Variables Demographic	Total cohort ($n=41$)	MIS-C ($n=20$)	Non-MIS-C ($n=21$)	p Value
Age				
1–5 years	24 (58.5)	12 (60.0)	12 (57.1)	0.89
5–12 years	17 (41.46)	8 (40.0)	9(42.8)	
Gender				
Male	26 (63.4)	12 (60.0)	14 (66.6)	0.66
Female	15 (36.5)	8 (40.0)	7 (33.3)	
Comorbidity	21 (51.2)	11 (55.0)	10 (47.6)	0.64
H/O contact with COVID patient	10 (25)	3 (15)	7 (33.3)	0.17
Clinical features				
Fever (>38°C)	31 (75.6)	20 (100)	11 (52.3)	**0.001**
Rash	8 (19.5)	7 (35)	1 (4.76)	**0.015**
Upper respiratory infection (URI)	5 (12.2)	1 (5.0)	4 (19.05)	0.16
LRTI	18 (43.9)	10 (50.0)	8 (38.1)	0.44
Acute gastro enteritis	5 (12.2)	5 (25)	0 (0.0)	**0.01**
Headache	5 (12.2)	5(25)	0	**0.01**
Seizures and/or Altered sense ruins	12 (29.2)	11 (55.0)	1 (4.7)	**<0.001**
Cardiac involvement	3 (7.3)	3 (15.0)	0	0.066
Renal Impairment	6 (14.6)	5 (25.0)	1 (4.76)	0.06
Shock	17 (41.4)	13 (65.0)	4 (19.05)	**0.003**
Respiratory failure	14 (34.1)	13 (65.0)	1 (4.7)	**<0.001**

Values are expressed as frequency (%). Bold values are statistically significant.

manifestations in MIS-C children were neurological symptoms and signs in the form of headache (25%), seizures and/or altered sensorium (55%) with p value <0.001. Out of 11 children, 10 had both seizures and altered sensorium while 1 had only seizures. Respiratory system involvement was seen in 50% of MIS-C cases. Rash was an associated finding in 35% of cases with significant p value < 0.01.

Gastrointestinal symptoms and signs were present in 25% of cases in the form of diarrhoea and vomiting with p value < 0.01 (Table 1).

In MIS-C children, 35% ($n=7$) presented with Acute Encephalitis-like illness, whereas 20% ($n=4$) were diagnosed with incomplete Kawasaki-like disease and 20% ($n=4$) had signs and symptoms of severe dengue-like illness (fever with rash with abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation and plasma leak and liver enlargement with shock and multiorgan dysfunction in later phase). Twenty percent ($n=4$) of children had pre-existing comorbidity along with COVID-like disseminated tuberculosis/tubercular meningitis(TBM) in three children and Spastic cerebral palsy in one child. One infant presented with Supraventricular tachycardia who showed a good response to adenosine therapy and recovered.

Lab parameters of MIS-C:

i. In total, 18 out of 20 cases of MIS-C had one or more of the inflammatory markers (CRP and serum ferritin) high with statistically significant p value of <0.001. IL-6 was done in three severe cases of MIS-C and was high in all. Hepatic dysfunction with elevation of liver enzymes were present in 12 out of 20 cases of MIS-C p value <0.007. Electrolyte abnormality seen in MIS-C cases were hyponatremia and/or hypokalaemia, found in 7 out of 20 children. Markers of Disseminated intravascular coagulation

Table 2. Lab parameters of COVID positive children (MIS-C & non-MIS-C)

Investigation	Total cohort	MIS-C ($n = 20$)	Non-MIS-C	p Value
Leucocytosis (12 – 10^9/l)	16 (39.02)	10 (50.0)	6 (28.5)	0.16
Leukopenia (<5 × 10^9/l)	11 (26.8)	3 (15.0)	8 (38.1)	0.10
Lymphopenia (<1.2 × 10^9/l)	11 (26.8)	6 (30.0)	5 (23.8)	0.65
Thrombocytopenia (<150 × 10^9/l)	11 (26.8)	5 (25.0)	6 (28.5)	0.80
Electrolyte abnormality (hyponatremia and/or Hypokalemia) S.Na^+ <130 mmol/l S. K^+ <3.5 mmol/l	7 (17.0)	7 (35.0)	0 (0.0)	**0.003**
High inflamatory marker (CRP and serum ferritin) CRP > 10 mg/l Serum ferritin >300 ng/ml	22 (53.6)	18 (99.0)	4 (19.05)	**<0.001**
Deranged urea/creatinine Urea > 20 mg/dl Creatinine > 1.2 mg/dl	2 (4.8)	1 (5.0)	1 (4.7)	1
Tissue markers (LDH and/or CPK-MB) LDH > 300 U/l CPK-MB > 25 U/l	10 (24.3)	7 (35)	3 (14.2)	**0.02**
Hepatic dysfunction AST > 50 U/l ALT > 50 U/l	16 (39.0)	12 (60.2)	4 (19.05)	**0.007**
Markers of DIC D-dimer > 250 ng/ml INR > 1.5	12 (29.2)	10 (50.0)	2 (9.5)	0.13
IL6 >20 pg/ml	3 (7.3)	3 (15.0)	0 (0.0)	**0.008**
CXR suggestive of LRTI	16 (39.02)	11 (55.0)	5 (23.8)	0.11

Values are expressed as frequency (%). Bold values are statistically significant.

(DIC) such as D-dimer and/or deranged coagulation profile were seen in 50% of cases (10/20). Serum lactate dehydrogenase (LDH) values were found to be high in 7 out of 20 cases. These changes in serum electrolytes, high inflammatory markers and tissue markers with elevation in liver enzymes were statistically significant in MIS-C cases (Table 2). Cerebrospinal fluid (CSF) examination was possible in eight children and none had findings suggestive of meningitis. In others CSF was not done due to hemodynamic instability or consent not available.

Central nervous system (CNS) imaging was done in nine children [Computed Tomography (CT) scan in eight and ultrasonography (USG) in one child]. Out of those three children had findings of subacute infarct in right parietooccipital region and left thalamus, Acute to subacute infarct in right middle cerebral artery territory and Oedema left frontotemporal region, respectively. All others had normal imaging.

Table 3. Outcome of COVID positive children (MIS-C & non-MIS-C)

Outcome(s)	MIS-C ($n = 20$)	Non-MIS-C ($n = 21$)	p Value	OR (95% CI)
Death	12 (60.0)	1 (4.7)	**<0.001**	30 (3.32–270.37)
Requiring O_2	18 (90.0)	7 (33.3)	**<0.001**	18 (3.22–100.48)
Requiring ventilation	13 (65.0)	1 (4.7)	**<0.001**	37.14 (4.08–338.10)

Values are expressed as frequency (%). Bold values are statistically significant.

Outcome and intervention

Most of non-MIS-C cases were stable and required only supportive therapy while most MIS-C cases were sick and needed intensive care treatment. Seven (33.3%) out of 21 non-MIS-C cases required oxygen supplementation compared to 90% of MIS-C cases which was statistically significant with odds ratio (OR) with 95% confidence interval (CI) of 18 (3.32–100.48; Table 3). One (4.7%) out 21 non-MIS-C cases required ventilatory and inotropic support while 65% of MIS-C required ventilation at or during hospitalization with 37.14 (4.08–338.10) OR and CI (Table 3). Steroids were used as an adjunctive therapy in 80% of the MIS-C cases. Sixty-five percent of the children went into shock and/or respiratory failure and required ionotropic support and invasive ventilation support. Four cases out of 20 children having Kawasaki-like illness were given IVIG as therapy. In total cohort of 41 children mean duration of illness was 10 days while survival rate was 68.3% ($n = 28$). Out of total 13 deaths among COVID positive children , 12 deaths were found in severe critical MIS-C cases as compared with 1 in non-MIS-C case with OR of 30 (3.32–270.37; Table 3).

DISCUSSION

Our study shows large incidence of MIS-C in hospitalized children with COVID-19. Neurological signs and symptoms as predominant presenting feature, median age <5 years, presence of tuberculosis as comorbidity, high rate of multiorgan dysfunction and death in our MIS-C group is different from what is being reported from around the world.

There is scanty literature on neurological presentation of MIS-C. As observed in data from USA and Europe [10, 14, 15], children fulfilling the criteria of MIS-C presented with varied and wide spectrum of disease [16] ranging from fever, rash, mild respiratory illness, gastrointestinal symptoms to severe disease like inflammatory vasculopathy and coagulopathy similar to Kawasaki-like disease and toxic shock syndrome. However, predominant finding in our study was the Encephalitis-like presentation with fever, seizure and altered sensorium in 35% of MIS-C patients. Regarding the case definition of MIS-C, CDC [9] and WHO [17] both have defined MIS-C as fever with multiorgan involvement and high inflammatory markers with no alternative diagnosis in COVID-confirmed cases. However, there is a slight difference with respect to the duration of fever (>24 h in CDC vs 3 days in WHO) and neurological manifestations (.not included in WHO case definition). Our study used CDC definition to have inclusion of all the possible manifestations of MIS-C cases.

In our study almost 60% of children presenting with MIS-C were <5 years. However, most of the studies have reported the median age of presentation of MIS-C to be > 5 years, with median ranging from 6 to 10 years in different studies [12, 18]. Though, typical KD presents in younger age group, almost 80% presents before 5 years [19]. There is a male preponderance, almost 60% of children with MIS-C are males as seen in other studies [18]. This highlights the need for high index of suspicion in children presenting in this age group with severe symptoms.

The reported incidence of any neurologic symptom and sign was 13% in 0–5 years and 38% in those 13–20 years of age [10]. In another meta-analysis of eight studies on clinical presentation in MIS-C, neurological symptoms were present in 22% of patients [18].

Another important finding was that 25% of children presented with hyperinflammatory coagulopathy, shock and multiorgan involvement. Three of them also had severe form of dengue-like illness with fever, pain abdomen, fluid overload and plasma leakage with shock and multiorgan dysfunction [20]. Dengue serology was negative in all these cases and had mild hepatomegaly and raised transaminases and high inflammatory markers.

In MIS-C cases, 20% (4/20) of the children had complete/incomplete Kawasaki-like illness in the form of fever, rash, conjunctival congestion and desquamation. However, 75% of the cases were associated with shock and required inotropic support. Similar finding is reported in a study in US children and adolescents where 5% of children with Kawasaki-like disease patients had shock, hyperinflammation and multiorgan involvement similar to KD Shock Syndrome [8, 15]. A case series of four patients from Mexico has also reported above findings like fever, rash, shock and myocardial involvement with severe disease [21].

In comorbidity along with MIS-C, three out of four children had tuberculosis (disseminated, military Koch and TBM in one each) while fourth child had spastic CP. Two of three children were diagnosed as tuberculosis at time of admission along with COVID, whereas third one was already on Anti-Tubercular Treatment. As published in literature clinical assessments to investigate COVID-19 (e.g. clinical picture, imaging, investigations) facilitate the identification of a probably pre-existing TB. Any contribution of COVID-19 to TB pathogenesis cannot be excluded or confirmed. Further studies need to be done to look for the role played by SARS-CoV-2 in the progression of TB infection to disease [22, 23]. Association of co morbidities like tuberculosis with COVID-19 is not very well described in paediatric population yet, highlighting the need for further studies on this.

As observed in various published literature [8, 10, 16, 24–26], most of our children with MIS-C also had multiorgan involvement with elevated markers of inflammation. MIS-C cases had neutrophilia, increased CRP, ferritin, troponin and D-dimer but lower lymphocytes and platelets.

As MIS-C in COVID-19 is a novel syndrome, no definitive treatment guidelines are as yet established but the major goals of treatment include decreasing systemic inflammation and improving organ function and reducing the risk of long-term sequelae [27].In most of the published data commonly used therapy in MIS-C patients is IVIG along with adjunctive high dose steroids [10, 26]. In our MIS-C cohort, four patients of Kawasaki-like disease were treated with IVIG along with steroids and all of them had good response to therapy. Steroids were used in 80% of MIS-C children however outcome was dependent on severity of illness at presentation. Almost 90% of our children required Paediatric ICU support and 65% required ventilatory support. In most other studies also, it was noted that children with MIS-C were critically ill and were managed in Paediatric ICU [28] and ventilation/intubation was required [12, 14, 15]. As found in our study, finding of severe form of the disease and a high number of MIS-C has also been shown in a multinational study in Latin American children in contrast to studies from China, Europe and North America [29].

Children with MIS-C have a higher mortality as, our hospital being a tertiary care referral hospital, most of the children enrolled in our study were being referred from other hospitals of Delhi and were in the severe spectrum of disease at the time of admission. As per thesis research work done at our department (still unpublished) about 20% mortality is seen among referred patients within 48 hours of hospital admission. Out of these highest referrals (32%) are in age group of 2-5 years [30].

No definite treatment guidelines were followed for management and probably they were picked up late due to lack of protocols for MIS-C at the satellite referral hospitals.

CONCLUSION

High index of suspicion for MIS-C in severe critical cases in the time of pandemic is the need of the hour. MIS-C may have different clinical presentations in different geographical areas.

Once organ dysfunction develops in the setting of severe inflammation outcome may be bad. Institutions must follow the protocol-based

guidelines guided by emerging worldwide evidence and review them periodically.

What this study adds

Acute Encephalitis syndrome-like illness could be a prominent presentation of MIS-C and require prompt intervention. Association of co-morbidities like tuberculosis with COVID-19 can be seen which need to be investigated further.

What this study lacks

Study with a bigger sample size with other hospitals of low middle-income countries and a more detailed work up for inflammatory markers, imaging in required cases and immunoglobulin testing in cases compatible with MIS-C presenting late with negative RTPCR are warranted for able to understand and frame guidelines regarding management of MIS-C cases.

AUTHOR'S CONTRIBUTIONS

S.G.: contributed to the design, acquisition, analysis of data and drafting the work. N.C.: contributed to the design, acquisition, analysis of data and drafting of work. A.S.: contributed to the acquisition of data; drafting of work. R.G.: contributions to the conception; revising it critically for important intellectual content. H.C. contributions to the conception and revising it critically for important intellectual content. R.M.P.: contributions to the statistical analysis and interpretation of data and revising it critically. B.S.A.: contributed to acquisition of lab data and revising critically for important intellectual content. All authors contributed to final approval of the version to be published; and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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