Original Research Article

Multisystem Inflammatory Syndrome in Children- A review

From a tertiary care centre in Maharashtra, India.

ABSTRACT:

Background:

A multisystem inflammatory syndrome in children (MIS-C) is associated with coronavirus disease 2019. Understanding the epidemiology and clinical course of multisystem inflammatory syndrome in children (MIS-C) and its tassociation with Covid-19 is important, given the clinical and public health implications of the syndrome.

Materials and Methods:

This was a prospective observational study carried out in the Department of Paediatrics, Krishna Institute Of Medical Sciences, Karad, Maharashtra, India, over a period of 12 months. Thirty three children, between the ages of 1 month-14 years were studied.

Results:

Out of the 67 patients admitted to our paediatrics ward during this period with suspected MISC, 35 patients were confirmed to have MIS-C on laboratory investigations. Involvement of a minimum of two systems was noted. The main clinical manifestations were gastrointestinal (abdominal pain, nausea and vomiting and diarrhoea) and dermatological (rash)**.** Fever was present in all 33 cases. The laboratory investigations were indicative of a pro inflammatory state seen in MIS-C. Positive findings on echocardiography were found in majority of cases.

Conclusion:

Multisystem inflammatory syndrome in children associated with SARS-CoV-2 has become serious public health problem in the paediatric population, with haemodynamic instability and cardiac dysfunction being the main signs, and rapid resolution with anti-inflammatory therapy.

Keywords: Anti-inflammatory, syndrome, coronavirus.

INTRODUCTION:

When the COVID-19 pandemic was first reported in Asia and initially spread throughout the globe, paediatricians were grateful that children were afflicted with mild symptoms in majority of the cases.[1-2] Then, an alarming warning came from the National Health Service in England in April 2020 about cases of older school-aged children and adolescents presenting to the ER with fever, hypotension, severe abdominal pain and cardiac dysfunction, resembling a Kawasaki like illness, who tested positive for SARS-CoV-2 infection either by nasopharyngeal RT-PCR assay or by antibody testing.[3] These children had laboratory findings of cytokine storm, including high serum IL-6 levels, and generally required inotropic support to increase cardiac output. Even though most of these children no longer required intensive care after only a few days and completely recovered, the health authorities were alerted to the possibility of an unusual presentation of SARS-CoV2 in the paediatric population. We describe the demographic characteristics, presenting symptoms, clinical course, laboratory findings, therapy received, and outcomes among children and adolescents meeting the case definition of MIS-C.

Physicians have noted some clinical similarities between MIS-C and Kawasaki disease (KD), a febrile illness of young childhood involving inflammation of the blood vessels that can result in coronary artery aneurysms. Patients with MIS-C may have some of the clinical features of KD, including fever, dilation of conjunctival blood vessels, rash and redness of the oropharynx. [4]However, these clinical signs can be observed in many infectious diseases in childhood and are not specific for any one diagnosis. The question has therefore arisen as to whether MIS-C and KD are the same entity.

MATERIALS AND METHODS:

Study design and patients:

This was a prospective observational study carried out in the Department of Paediatrics, Krishna Institute Of Medical Sciences, Karad, Maharashtra, India, over a period of 12 months (May-2020 to May-2021).

Case definition [5]:

CDC case definition
All 4 criteria must be met:
1. Age <21 years
2. Clinical presentation consistent with MIS-C, including **all** of the following:

- Fever:
  - Documented fever >38.0°C (100.4°F) for ≥24 hours
  - **or**
  - Report of subjective fever lasting ≥24 hours

- Laboratory evidence of inflammation
  - Including, but not limited to, **any** of the following:
    - Elevated CRP
    - Elevated ESR
    - Elevated fibrinogen
    - Elevated procalcitonin
    - Elevated D-dimer
    - Elevated ferritin
    - Elevated LDH
    - Elevated IL-6 level
    - Neutrophilia
    - Lymphocytopenia
    - Hypoalbuminemia

- Multisystem involvement
  - **2 or more** organ systems involved:
    - Cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia)
    - Respiratory (eg, pneumonia, ARDS, pulmonary embolism)
    - Renal (eg, AKI, kidney failure)
    - Neurologic (eg, seizure, stroke, aseptic meningitis)
    - Hematologic (eg, coagulopathy)
    - Gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal

bleeding) o Dermatologic (eg, erythroderma, mucositis, other rash)
▪ Severe illness requiring hospitalization
3. No alternative plausible diagnoses
4. Recent or current SARS-CoV-2 infection or exposure
▪ **Any** of the following: • Positive SARS-CoV-2 RT-PCR • Positive serology • Positive antigen test • COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Reference range used for laboratory investigations:

PARAMETER	***REFERENCE RANGE***
Haematology	
White blood cell count(10^3 ul)	4.0-12.0
Lymphocyte(%)	25-33
Neutrophil (%)	54-62
Hemoglobin (g/dL)	11.5-14.5
Platelets (10^3/mL)	150-450
Liver and renal function	
Albumin (g/dL)	4.0-5.3
Creatinine (mg/dL)	0.22-0.59
Alanine transaminase (U/L	5-45
Aspartate aminotransferase (U/L)	15-50
Inflammatory Markers	
C-reactive protein (mg/L)	Male 0.6-7.9 Female 0.5-10.0
Ferritin (ng/mL)	10-60
Procalcitonin (ng/mL)	<0.15
Lactate dehydrogenase (U/L)	150-500
Interleukin-6 (pg/mL)	<1.8
Creatine kinase (U/L)	5-13
Coagulation	
D-dimer(mg/ml)	<0.4

Erythrocyte Sedimentation Rate(mm/hr)	0-20
Cardiac	
Troponin (ng/L)	<10
Prohormone of brain natriuretic peptide (ng/L)	0-450

Reference (Ref.) ranges were obtained from Nelson Textbook of Pediatrics (we chose eight years as the age category provided the overall mean of included patients).

RESULTS:

Case testing and demographic characteristics: (Table 1)

Out of the 67 patients admitted to our paediatrics ward during this period with suspected MISC,35 patients were confirmed to have MIS-C on laboratory investigations, Majority of the cases (70%) were diagnosed on antibody testing (IgG,IgM antibodies). Only 30% of the cases were diagnosed on the basis of RT-PCR and Rapid Antigen Test.(Table 1)

The median age of children affected in our study is 8.6 years.No specific sex predilection was seen. Children in the age group of 0-5 years comprised 39% of the population and those in the age bracket of 6-14 years of age were 61%. In our study population,51% of males were affected and 49% females were affected.(Table 1)

Clinical features and involvement: (Table 1)

Most patients (78%) had involvement of at least two organ systems (Table 1). The most commonly involved organ systems were the gastrointestinal (69%), cardiovascular(57%); dermatological(68%). Fever with/without chills was present in 100% of cases. The main manifestations in clinical symptomatology were gastrointestinal and dermatological. Headache was the primary neurological symptom noted,seen in 0.2% of the cases. Lower respiratory symptoms primarily consisted of cough which was present in 54% of the overall cases.

Vital signs: (Table 2)

Median heart rate was noted to be 133 beats per minute,with tachycardia being noted at the time of admission in the majority of cases (96%). Hypotension was defined according to age appropriate criteria and it was seen in 70% of overall cases. Temperature, recorded with a digital thermometer in the right axilla, was found to be elevated (>38 degree Celsius) in 100% of the cases.The median oxygen saturation was found to be 98% (interquartile range 97-100%), with oxygen saturation <92% found only in 0.1 % of the cases.

Laboratory Investigations: (Table 2)

On admission, among patients with suspected or confirmed MIS-C, the median white-cell count was 10,100 per microliter, and 23 of 33 (69%) had lymphopenia; 26 of 33 (78%) had elevated proBNP levels, 15 of 33 (45%) had elevated troponin levels, 31 of 33 (93%) had elevated C-reactive protein levels, and 28 of 33 (84%) had elevated d-dimer levels (Table 2).

During hospitalization, at least one echocardiogram was obtained for 19 patients (57%); 12 (63%) had some degree of ventricular dysfunction, 6 (31%) had pericardial effusion, and 1 (0.05%) had a documented coronary-artery aneurysm. Additional clinical and laboratory findings on admission, according to age group, are provided in Table 2.

Clinical course and Outcomes: (Table 3)

The median time from symptom onset to hospital admission was 4 days,with 24 of 33 (72%) patients requiring ICU admission. A total of 28 patients (84%) received intravenous immune globulin (IVIG), 63 (90%) received systemic glucocorticoids, and 12 (36%) received vasopressor support; 28 (84%) received both systemic glucocorticoids and IVIG. Additional outcomes have been described in Table 3.

DISCUSSION:

We describe 33 patients younger than 14 years of age who met the criteria for MIS-C associated with SARS-CoV-2 infection. The majority of patients (70%) had laboratory-confirmed antecedent or concurrent SARS-CoV-2 infection, and most had no documented underlying conditions. Cardiovascular involvement was common, with almost half receiving vasopressor or vasoactive support and 1 in 12 having coronary-artery aneurysms. Most patients were cared for in an intensive care unit, and 20% received invasive mechanical ventilator support. Although most discharged patients survived,2 patients (0.05%) died, 2 of whom had previously been healthy.

Evidence supporting a causal link with SARSCoV-2 includes a strong temporal association with Covid-19 activity, confirmation of SARS-CoV-2 infection through nucleic acid or antibody testing in the majority of patients, and hyperinflammatory manifestations similar to those in adults with Covid-19.[6-8] Almost one third of the patients tested negative for SARS-CoV-2 by RT-PCR but had detectable antibodies.

We found variations in presenting symptoms and manifestations according to age. The prevalence of dermatologic symptoms was highest among children 0 to 5 years of age, and the prevalence of myocarditis (diagnoses and clinical) was highest among the adolescents. The prevalence of gastrointestinal symptoms was high in all age groups.

These patients met a case definition developed by the CDC that was designed to be sensitive.8 although more than one third of the patients had Kawasaki's disease–like clinical features, 60% of the patients would not have met complete or incomplete criteria for Kawasaki's disease.[9-10]

Although both Kawasaki's disease and MIS-C can have cardiovascular involvement, the nature of this involvement appears to differ between the two syndromes. We observed cardiovascular involvement leading to vasopressor or vasoactive support as a common and severe subphenotype, most frequently in older children and adolescents. Approximately 5% of children with Kawasaki's disease in the United States present with cardiovascular shock leading to vasopressor or inotropic support, [10] as compared with 50% of the patients in our series. Myocardial dysfunction is a prominent extrapulmonary manifestation of Covid-19 that has been associated with increased mortality in adults.[11-12]

Consistent with the diagnosis of MIS-C, multiple inflammatory markers were elevated. Examining the trends of some of these values may provide biologic insight to the disease or

may serve as potential predictors of MIS-C outcomes. In particular, the following analytes were elevated proBNP, elevated IL-6 and D-dimer.[14-15]

Understanding the pathogenesis of MIS-C will be necessary to inform clinical management and prevention efforts.[13] in our case series, a majority of patients were treated with immunomodulatory drugs, most commonly intravenous immune globulin (84%) and systemic glucocorticoids (90%). Vasopressors were also used. The use of these three agents suggests a pro inflammatory state, with slight similarities to Kawasaki Disease and toxic shock syndrome.[16]

CONCLUSION:

Although most children have mild or no illness from SARS-CoV-2 infection, MIS-C may follow Covid-19 or asymptomatic SARS-CoV-2 infection. Recognition of the syndrome and early identification of children with MIS-C, including early monitoring of blood pressure and electrocardiographic and echocardiographic evaluation, could help in the timely institution of appropriate supportive care and other potential therapeutic options. As children present with mild symptoms of Covid-19 and are less frequently tested than adults, the incidence of MIS-C among children infected with SARS-CoV-2 is unclear. It is essential to establish proper surveillance and maintain a high degree of suspicion, especially in areas where the transmission of SARS-CoV-2 is high.

TABLE 1: CLINICAL CHARACTERISTICS OF THE PATIENTS AT HOSPITAL ADMISSION, ACCORDING TO AGE GROUP

Characteristic	Overall(33)	0-5 years(13)	6-14 years(20)
Sex predilection			
Male	12	5	7
Female	11	6	5
Positivity for SARS-CoV-2 -no.			
On RT-PCR assay	11	4	7
On serologic assay for IgG antibodies	22	13	9
Symptoms at admission — no.			
Constitutional: fever or chills	33	9	24
Cardiovascular: chest pain	3	1	2
Gastrointestinal			
Abdominal pain	23	10	13
Nausea or vomiting	24	9	15
Diarrhoea	21	13	8
Dermatologic			
Rash	26	15	11
Swollen hands or feet	4	2	2

Mucocutaneous			
Conjunctivitis	16	9	7
Mucosal changes	14	6	8
Neurologic			
Headache	6	2	4
Altered mental status or confusion	1	0	1
Lymphadenopathy	5	3	2
Musculoskeletal			
Muscle aches or myalgias	8	2	6
Joint pain	3	1	2
Upper respiratory			
Congestion	12	8	4
Sore throat	7	3	4
Lower respiratory			
Cough	18	8	10
Shortness of breath	7	3	4
Wheezing	1	1	0

TABLE 2: VITAL SIGNS AND LABORATORY VALUES OF THE PATIENTS AT HOSPITAL ADMISSION, ACCORDING TO AGE GROUP.

Characteristic	**Overall(33)**	**0-5 years(13)**	**6-14 years(20)**
Vital signs			
Median heart rate (IQR) — beats/min	133 (120–148)	140 (130–158)	128 (123–153)
Tachycardia — no.	32	11	20
Hypotension	23	6	17
Temperature ≥38.0°C — no.	33	9	24
Median oxygen saturation (IQR)	98 (97–100)	98 (96–99)	99 (97–100)
Oxygen saturation <92%	4	3	1

Laboratory values			
Median white-cell count (IQR) - ×10−3/μl	10.1(6.6–13.5)	11.8 (7.4–14.8)	9.7 (6.4–13.7)
Lymphopenia — no. /total no.	23/33	7/13	16/20
Neutropenia — no./total no.	0/33	0/13	0/20
Platelet count <80x10--3/μl	7/33	5/33	2/33
Elevated proBNP level — no. /total no.	26/33	9/13	17/20
Elevated troponin level — no. /total no.	15/33	6/13	9/20
Elevated C-reactive protein level	31/33	12/13	18/20
D-dimer level >0.55 mg/liter — no./total no.	28/33	11/13	17/20
Ferritin level >300 ng/ml — no./total no.	22/33	12/13	10/20
LDH level ≥500 U/liter — no./total no.	3/33	1/13	2/20
Interleukin-6 level ≥5.0 pg/ml — no./total no.	12/33	7/13	6/20
ESR ≥40 mm/hr — no./total no. (%)	24/33	8/13	16/20
Echocardiography:			
Left Ventricular dysfunction	12	4	8
Pericardial Effusion	6	1	5
Corornary artery aneurysms	1	0	1

<u>TABLE 3:</u> CLINICAL COURSE AND OUTCOMES, ACCORDING TO AGE GROUP.

Characteristic	**Overall(33)**	**0-5 years(13)**	**6-14 years(20)**
Median time from symptom onset to hospital admission	4 (3–6)	4 (3–6)	4 (3–6)

(IQR) — days			
ICU admission — no.	24	12	12
Median length of stay (IQR) — days	6.0 (4.0–9.0)	6.0 (3.0–8.0)	6.0 (4.0–10.0)
Therapy — no.			
CPAP	13	6	7
Mechanical Ventilation	4	3	1
Vasopressor support	12	4	8
Systemic glucocorticoids	30	11	19
IVIG	28	16	12
Clinical Outcomes-No.			
Shock	12	6	7
Myocarditis	10	4	6
Acute kidney injury	11	7	4
Death	2	1	1

REFERENCES:

1. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr 2020 April 22 (Epub ahead of print).

2. Lu X, Zhang L, Du H, et al. SARSCoV-2 infection in children. N Engl J Med 2020; 382:1663-5.

3. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 395:1607-8.

4. Dominguez SR, Friedman K, Seewald R, Anderson MS, Willis L, Glodé MP. Kawasaki disease in a pediatric intensive care unit: a case-control study

5. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). May 14, 2020 (https://emergency.cdc.gov/ han/2020/han00432.asp).

6. 4. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med 2020; 382: 2372-4. 25.

7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497-506. 26.

8.Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020 March 12 (Epub ahead of print).

9. Shackelford PG, Strauss AW. Kawasaki syndrome. N Engl J Med 1991; 324:1664-6.

10. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and longterm management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017; 135(17):e927-e999.

11. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 March 27 (Epub ahead of print).

12. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020 March 25 (Epub ahead of print).

13. Multisystem Inflammatory Syndrome in Children (MIS-C), a Post-viral Myocarditis and Systemic Vasculitis—A Critical Review of Its Pathogenesis and Treatment-Jeremy C. McMurray 1 , Joseph W. May 1,2,3 , Madeleine W. Cunningham 4 and Olcay Y. Jones

14. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin,interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 2001; 164(3):396–402. doi: 10.1164/ajrccm.164.3.2009052.

15. Grifoni E, Valoriani A, Cei F, et al. Interleukin-6 as prognosticator in patients with COVID-19. J Infect 2020; 81(3):452–82. doi: 10.1016/j.jinf.2020.06.008.

16.Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA 2020 June 8 (Epub ahead of print).