



Comparison of Multisystem Inflammatory Syndrome (MIS-C) and Dengue in Hospitalized Children

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Abstract

Objective Multisystem inflammatory syndrome (MIS-C) in children is a febrile illness that has overlapping presentation with other locally prevalent illnesses. Clinicolaboratory profile of children admitted with MIS-C and dengue were compared to understand their presentation at the outset.

Methods This was a retrospective study of children ≤ 12 y admitted with MIS-C (WHO definition) or laboratory-confirmed dengue between August 2020 and January 2021 at a tertiary center in North India.

Results A total of 84 children (MIS-C - 40; dengue - 44) were included. The mean (SD) age [83.5 (39) vs. 91.6 (35) mo] was comparable. Rash (72.5% vs. 22.7%), conjunctival injection (60% vs. 2.3%), oral mucocutaneous changes (27.5% vs. 0) and gallop rhythm (15% vs. 0) were seen more frequently with MIS-C, while petechiae [29.5% vs. 7.5%], myalgia (38.6% vs. 10%), headache (22.7% vs. 2.5%), and hepatomegaly (68.2% vs. 27.5%) were more common with dengue. Children with MIS-C had significantly higher C-reactive protein (124 vs. 3.2 mg/L) and interleukin 6 (95.3 vs. 20.7 ng/mL), while those with dengue had higher hemoglobin (12 vs. 10.2 g/dL) lower mean platelet count (26 vs. $140 \times 10^9/L$), and greater elevation in aspartate (607 vs. 44 IU/L) and alanine (235.5 vs. 56 IU/L) aminotransferases. The hospital stay was longer with MIS-C; however, PICU stay and mortality were comparable.

Conclusion In hospitalized children with acute febrile illness, the presence of mucocutaneous features and highly elevated CRP could distinguish MIS-C from dengue. The presence of petechiae, hepatomegaly, and hemoconcentration may favor a diagnosis of dengue.

Keywords Dengue · MIS-C · PIMS-TS · COVID-19 · SARS-CoV-2

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Introduction

While the world battled the start of SARS-CoV-2 pandemic in 2020, pediatricians across the globe were relieved of the early burden, as the virus seemed to cause a less severe illness in children [1]. Similar trends were observed in Indian children [2, 3]. Several mechanisms were proposed for this differential severity in children including cross-reactive immunity to common coronaviruses, lower density and affinity of angiotensin-converting enzyme 2 (ACE-2) receptors, higher comorbidities in adults and a lower intensity of exposure in children, among others [4]. While researchers were busy trying to explain these mechanisms, a new illness labelled as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C)

started to emerge exclusively in children and adolescents, weeks after exposure to the SARS-CoV-2 virus [5–9]. This syndrome resembled Kawasaki disease in some of its manifestations but also had some distinct features. High-grade fever, rash, conjunctival injection and gastrointestinal symptoms were common presenting manifestations. Investigations usually revealed elevated serum markers of systemic inflammation along with one or more organ dysfunctions. The syndrome seemed to affect the heart disproportionately more causing myocardial dysfunction and cardiogenic shock [5–7].

While SARS-CoV-2 wreaked havoc everywhere, seasonal epidemics of various infectious diseases continued. Dengue is one such viral illness, seen during and following the rainy seasons in various parts of the world. The clinical spectrum of dengue consists of a biphasic fever with abdominal pain, thrombocytopenia, features of plasma leakage, circulatory shock, and multiorgan dysfunction. The severity may range from a mild undifferentiated febrile illness to severe multiorgan dysfunction syndrome [10]. It is well established that tropical infections like dengue, scrub typhus, malaria, enteric fever, and leptospirosis may present with overlapping features prompting the adoption of a broader syndromic approach at the outset [11].

MIS-C with the clinical presentation of fever, pain abdomen, rash, and organ dysfunction may pose diagnostic difficulty with severe dengue and other tropical infections. During overlapping coepidemics of these illnesses, it may become even more difficult to make a specific diagnosis at admission. This may hamper the outcome of these diseases, as management strategies are different. Cases of diagnostic dilemma between MIS-C and dengue have been reported recently [12]. The national vector-borne disease control program (NVBDCP), India has published a guideline for dengue case management during COVID-19 pandemic in October 2020 [13]. The authors believe that the comparison of epidemiology, and clinical and laboratory profile of dengue and MIS-C would help in better discrimination of these illnesses in children and help clinicians to arrive at a diagnosis at the outset. Hence, the case records of children hospitalized with a diagnosis of dengue and MIS-C were retrospectively evaluated, and their clinicolaboratory profile and outcome were compared.

Materials and Methods

This was a retrospective study of patients admitted between August 2020 and January 2021 at the pediatric emergency and intensive care units of a tertiary care teaching hospital in North India. Children aged 12 y or younger admitted with a diagnosis of dengue fever or MIS-C were enrolled. Dengue

was diagnosed by detection of NS1 antigen (SD Biosensor, India) or presence of IgM anti-dengue antibodies using Mu capture ELISA (NIV, ICMR, Pune, India) in children with clinically compatible illness. Diagnosis of MIS-C was established in children fulfilling WHO criteria after exclusion of other causes [14]. All children were tested for acute and/or recent SARS-CoV-2 infection by RT-PCR and detection of IgG antibodies against SARS-CoV-2 using semiquantitative micro-ELISA (EUROIMMUN kit). Case records were reviewed for data collection. The baseline demographic and clinical data including presenting clinical symptoms and signs were recorded. Laboratory parameters at admission, including hemoglobin (Hb), platelet count, white blood cell (WBC) count, serum albumin, liver function tests (alanine aminotransferase and aspartate aminotransferase) and renal function tests (urea, creatinine) were recorded. Interleukin 6 (IL-6) was measured through cytometric bead array (BD biosciences) and interleukin 8 (IL-8) was measured through micro-ELISA (Sigma-Aldrich). Details of supportive care such as mechanical ventilation, vasoactive drug therapy, and hospital outcome including length of pediatric intensive care unit (PICU) stay, hospital stay, and mortality were noted.

Data entry was done into Microsoft Excel 2020 (Microsoft, Redmond, WA, USA) and statistical analysis was performed using SPSS software version 22 (IBM Corp. 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA). Categorical variables were described as percentages. Continuous variables were described as mean and standard deviation or median and interquartile range based on normality of distribution. Proportions were compared between groups using chi-square test or Fisher exact test, whichever applicable. Numerical variables were compared between the two groups by Student *t*-test or Mann–Whitney *U* test, depending upon normality of distribution. A *p* value < 0.05 was considered significant.

Results

A total of 84 children were admitted with either dengue ($n = 44$) or MIS-C ($n = 40$) during the study period between August 2020 and January 2021. The temporal distribution of cases is depicted in Fig. 1. The mean age and sex distribution were comparable between the dengue and MIS-C groups. Fever at presentation was common, seen in almost all (98%) in both the groups. Rash [73% vs. 23% ($p < 0.0001$)], conjunctival injection [60% vs. 2.3% ($p < 0.0001$)], diarrhea [30% vs. 11.4% ($p < 0.029$)], and oral mucosal changes [27.5% vs. 0 ($p < 0.0001$)] were seen more frequently in children with MIS-C while petechiae [29.5% vs. 7.5% ($p = 0.01$)], myalgia [38.6% vs. 10% ($p = 0.002$)], headache [22.7% vs. 2.5% ($p = 0.006$)], vomiting [72.7% vs. 50% ($p = 0.04$)], and

Overlap of Dengue and MIS-C cases

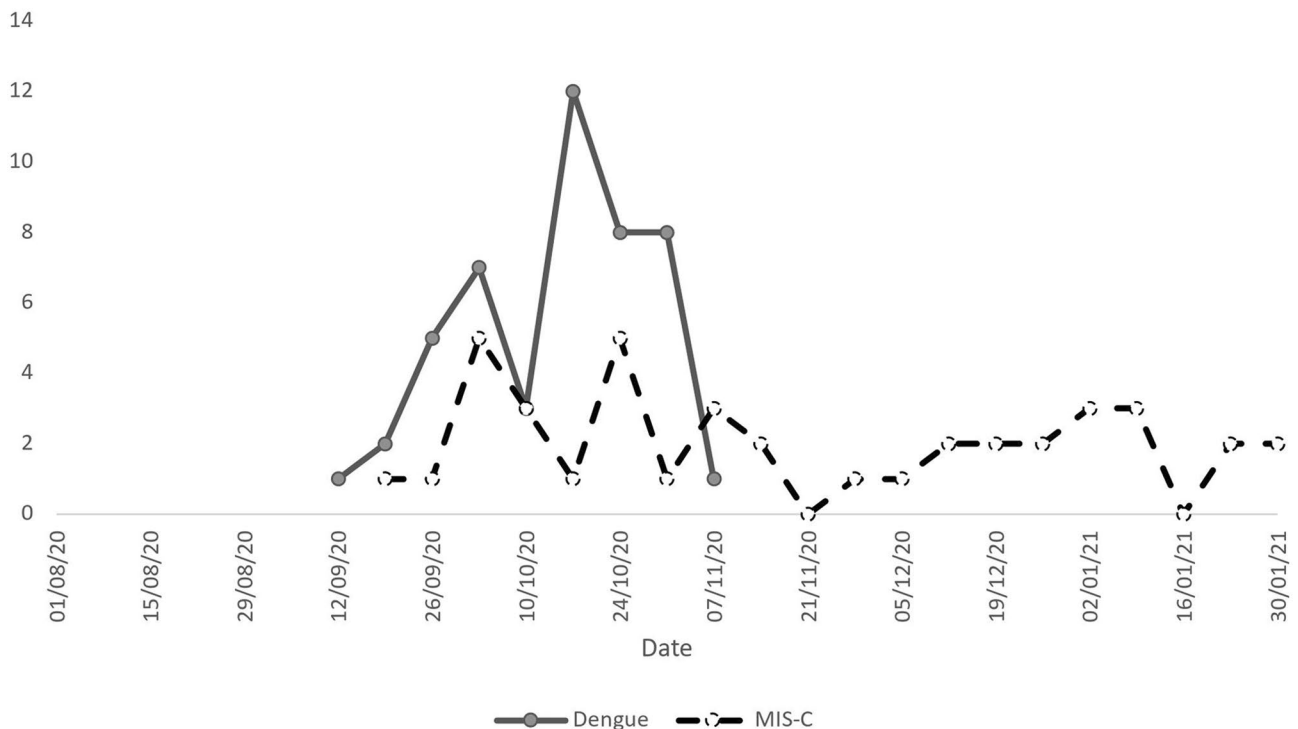


Fig. 1 Overlap of dengue and MIS-C cases during the study period

hepatomegaly [68.2% vs. 27.5% ($p < 0.0001$)] were significantly more common in children with dengue (Table 1). A gallop rhythm on auscultation was identified exclusively in children with MIS-C [15% vs. 0% ($p = 0.008$)] (Table 1). Hemoglobin at admission was significantly higher in children with dengue [12 vs. 10.2 g/dL ($p = 0.001$)] while platelets were markedly lower [26 vs. 140×10^9 cells/L ($p < 0.0001$)]. Total leukocyte count (TLC) and absolute neutrophil counts (ANC) had a trend towards higher values in children with MIS-C while absolute lymphocyte counts (ALC) were low but comparable to dengue (Table 2). Aspartate aminotransferase and alanine aminotransferase were elevated significantly more in children with dengue. C-reactive protein (CRP) [124 vs. 3.2 mg/L ($p < 0.0001$)] and interleukin 6 [95.3 vs. 20.7 pg/mL ($p = 0.006$)] were significantly higher in the MIS-C group, while IL-8 levels [23.4 vs. 23.4 pg/mL ($p = 0.327$)] were comparable between the two groups (Table 2). Shock was identified in 45.5% in the dengue group and 42.5% in MIS-C group at admission. Children with MIS-C received vasoactive support more often than children with dengue ($p = 0.05$). Hepatic dysfunction was seen more frequently in dengue, while the incidence of other organ dysfunctions, need for renal replacement therapy, invasive ventilation, length of PICU, and mortality were comparable between the two groups. Children with MIS-C had a longer stay in the hospital (Table 1).

Discussion

In this retrospective comparative analysis, although dengue and MIS-C shared several features, differing frequencies of certain clinical and laboratory features were found, which could discriminate them at presentation. Conjunctival and oral mucosal changes were seen almost exclusively in children with MIS-C. Rash was thrice more common in MIS-C than in dengue. However, the presence of petechiae or skin bleed is more likely to be seen with dengue. Changes in the extremities were nonspecific as both the diseases presented with peripheral edema. Gastrointestinal (GI) features were reported to be very common (80%–90%) in MIS-C, and identified as an important clue to diagnosis of this inflammatory syndrome [15, 16]. However, GI symptoms were found to be less helpful in distinguishing MIS-C from dengue. Abdominal pain is an important early warning sign in severe dengue and has been reported in 30%–50% of the hospitalized children [17, 18]. Loose stool, although less common in dengue, is reported in 5%–15%, particularly in infants and young children [17, 18]. Both dengue and MIS-C, if severe, are likely to present with circulatory shock. About 40%–45% of children were noted in each group to present in shock. A fluid bolus was the early intervention in many of them, though children with MIS-C were more often

Table 1 Comparison of clinical profile and outcomes

	Dengue (n = 44)	MIS-C (n = 40)	p value	OR
Age (months)	91.6 (35)	83.5 (39)	0.316	
Sex (boys)	27 (61.4%)	26 (65%)		
History of SARS-CoV-2 contact	0	5 (12.5%)	0.021	2.26 (1.76–2.89)
Fever	43 (97.7%)	39 (97.5%)	0.946	
Rash	10 (22.7%)	29 (72.5%)	<0.0001	2.61 (1.58–4.32)
Conjunctival injection	1 (2.3%)	24 (60%)	<0.0001	3.54 (2.31–5.42)
Petechiae	13 (29.5%)	3 (7.5%)	0.01	1.78 (1.25–2.53)
Myalgia	17 (38.6%)	4 (10%)	0.002	1.89 (1.33–2.69)
Headache	10 (22.7%)	1 (2.5%)	0.006	1.95 (1.43–2.66)
Edema	14 (31.8%)	7 (17.5%)	0.13	
Pain abdomen	30 (68.2%)	23 (57.5%)	0.311	
Vomiting	32 (72.7%)	20 (50%)	0.044	2.53 (1.02–6.31)
Diarrhea	5 (11.4%)	12 (30%)	0.029	1.72 (1.13–2.63)
Oral mucosal changes	0	11 (27.5%)	<0.0001	2.52 (1.90–3.34)
Lymphadenopathy	2 (4.5%)	2 (5%)	0.902	
Hepatomegaly	30 (68.2%)	11 (27.5%)	<0.0001	5.46 (2.13–14.00)
Splenomegaly	1 (2.3%)	1 (2.5%)	0.931	
Gallop rhythm	0	6 (15%)	0.008	2.29 (1.78–2.95)
Shock at admission	20 (45.5%)	17 (42.5%)	0.785	
Fluid bolus at admission	19 (43.2%)	14 (35%)	0.345	
Vasoactive/Inotrope infusion	17 (38.6%)	24 (60%)	0.050	1.57 (0.99–2.51)
PICU admission	19 (43.2%)	34 (85%)	0.007	1.98 (1.15–3.40)
Acute kidney injury	11 (25%)	18 (45%)	0.120	
Liver dysfunction	25 (56.8%)	9 (22.5%)	0.001	1.94 (1.29–2.91)
Invasive ventilation	10 (22.7%)	9 (22.5%)	0.97	
Renal replacement therapy	4 (9%)	0	0.051	2.0 (1.61–2.49)
Length of PICU stay	5 (2–11)	5 (2–8)	0.373	
Length of hospital stay	4 (3–6)	7 (4–9)	<0.0001	
Mortality	4 (9%)	2 (5%)	0.457	

Values are expressed in numbers (%), mean (standard deviation) or median (interquartile range)

treated with inotrope/vasoactive agent infusion during the course of their hospital stay.

MIS-C being a diagnosis of exclusion poses challenges to the emergency physician in discriminating it from other common febrile illnesses. Carlin et al. in a cohort of 232 children including 44 children with MIS-C, attempted to differentiate them from children presenting to outpatient clinics with other febrile illnesses [19]. None of the controls required admission in their cohort, a limitation which was overcome in the present study as only admitted patients were evaluated for recruitment. Their findings of increased incidence of rash, conjunctivitis, and oral mucosal changes in MIS-C as compared to other febrile illnesses, is in concordance with the present study. Their finding of increased incidence of thrombocytopenia in MIS-C was not replicated in the present study, as dengue itself is associated with severe thrombocytopenia. Leukopenia and lymphopenia are also common features in dengue. This might explain why ALC was comparable between the two groups, while TLC and

ANC tended to be higher in the MIS-C cohort in the present study. In the study by Carlin et al., children with MIS-C had highly elevated CRP compared to other febrile controls, a finding also replicated in another smaller cohort by Kelly et al. [19, 20]. In the present cohort too, children with MIS-C had significantly higher CRP, a marker that can distinguish it from dengue.

Both over- and underdiagnosis of MIS-C may be harmful. Overdiagnosis may lead to unwarranted use of steroids, intravenous immunoglobulins, and other immunomodulators, which may actually worsen an infective febrile illness [21, 22]. Underdiagnosis and a delayed diagnosis may lead to delay in initiating immunomodulatory therapy, persistent inflammatory state, and worsening organ dysfunction [23]. There might be some cases of dengue fever, with past exposure to SARS-CoV-2, who might have a positive anti-SARS-CoV-2 antibody titer, but do not fulfill the criteria for a diagnosis of MIS-C. In another study from the authors' center, it was reported that these children may have a less

Table 2 Comparison of laboratory profile

	Dengue (<i>n</i> = 44)	MIS-C (<i>n</i> = 40)	<i>p</i> value
SARS-CoV-2 exposure			
RT-PCR positive	0	4	
IgG positive	15	20	
Both RT-PCR and IgG positive	0	1	
Hemoglobin (g/dL)	12 (2.4)	10.2 (2.1)	0.001
Total leucocyte count ($\times 10^9$ cells/L)	8.5 (4.9–11.7)	10.3 (5–16.3)	0.068
Absolute neutrophil count ($\times 10^9$ cells/L)	3.6 (2.9–8.1)	8.3 (3.7–13.3)	0.070
Absolute lymphocyte count ($\times 10^9$ cells/L)	2.1 (1.3–2.8)	1.5 (0.8–2.8)	0.288
Platelet count at admission ($\times 10^9$ cells/L)	26 (16–47)	140 (70–210)	<0.0001
Aspartate transaminase (IU/L)	607 (161.5–1470)	44 (27.5–120.5)	<0.0001
Alanine transaminase (IU/L)	235.5 (66–616.8)	56 (27.5–106)	<0.0001
Albumin (g/dL)	2.5 (0.7)	2.6 (0.6)	0.406
CRP (mg/L)	3.2 (1.2–17.9)	124 (21–204)	<0.0001
IL-6 (pg/mL)	20.7 (11.1–67.4)	95.3 (25.5–638.2)	0.006
IL-8 (pg/mL)	23.4 (22.5–25.0)	23.4 (22.5–29.8)	0.327

Values are expressed in numbers (%), mean (standard deviation) or median (interquartile range)

severe course of dengue fever [24]. The surge of cases of SARS-CoV-2 in India is expected to be followed in its wake by a surge in cases of MIS-C. “MIS-C or not MIS-C” will thus be a valid conundrum when a febrile patient presents to the hospital. The present comparative analysis tries to answer this question in relation to dengue fever. The strength of the present study is in its attempt to differentiate between the two illnesses with similar presentations based on both clinical and laboratory parameters. Such differentiation of dengue and MIS-C will be the need of the hour during potential coepidemics in dengue-prevalent areas like Southeast Asia and South America. The limitation of the present study is that it is a single-center retrospective study with a limited sample size.

Conclusions

In hospitalized children with acute febrile illness, the presence of mucocutaneous features and highly elevated CRP could distinguish MIS-C from dengue. The presence of petechiae, hepatomegaly and hemoconcentration may favor a diagnosis of dengue.

Authors' Contributions KN and SKA conceptualized the study; MSR, NR, and PA collected and recorded the data; MSR, SKA, and KN drafted the manuscript; MK, AG, RKR, and RWM provided lab support and proofread the manuscript; RMK, AB, and MJ supervised the study and approved the final manuscript. MJ will act as the guarantor for this paper.

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Declarations

Conflict of Interest None.

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