Severity and Cardiac Involvement in Multisystem Inflammatory Syndrome in Children

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Abstract
Multisystem inflammatory syndrome in children (MIS-C) occurs secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A retrospective study, involving 6 tertiary-care centers in Haryana, was conducted to evaluate the clinical features, severity, laboratory findings, and outcomes of patients with MIS-C. Disease severity was graded (mild/moderate/severe) and presence of cardiac abnormalities noted. Patients with and without cardiac abnormalities and with and without severe disease were compared. Forty-eight children with MIS-C were included (median age - 9.5 y). Fever (100%), gastrointestinal (83.3%) and mucocutaneous (50%) symptoms were common. Only 16.7% patients had previous history of documented SARS-CoV-2 infection/contact. Severe disease and cardiac abnormalities were seen in 47.9% and 54.2% patients, respectively. NT-proBNP > 1286.5 pg/mL and thrombocytopenia (≤ 119500/µL) were significant risk factors for severe MIS-C. Forty-five patients (93.8%) recovered and 3 died. Median hospitalization duration was 7 d (5–9.5). MIS-C must be considered as a possibility in any febrile child, even if a positive epidemiological history is absent. High NT-proBNP and thrombocytopenia are significant risk factors for severe MIS-C.

Trial Registration The study was registered with the Clinical Trials Registry, India (CTRI/2021/09/036491).

Keywords Multisystem inflammatory syndrome in children · Pediatric · SARS-CoV-2 infection

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a novel condition identified following the SARS-CoV-2 pandemic. In this paper, the clinical pattern of MIS-C in children from urban Haryana is described. The objectives of the present study were: (1) evaluation of clinical and laboratory characteristics of hospitalized MIS-C patients, including disease severity, therapeutic interventions, and outcomes; (2) comparison of patients with and without severe disease, and with and without cardiac involvement; and (3) identification of risk factors for severe MIS-C.

Material and Methods

A retrospective multicentric observational study was conducted in 6 tertiary-care hospitals in urban Haryana. Hospitalized patients (age < 18 y) fulfilling the WHO-MIS-C criteria were included [1]. Those with concomitant infections were excluded. Demographic details,
symptomatology, laboratory investigations, treatment, and outcomes were noted. Cardiac abnormality was defined as elevated N-terminal-pro-B-type brain natriuretic peptide (NT-proBNP), presence of moderate/higher valvular regurgitation, pericardial effusion, ejection fraction < 50%, dilated coronary segment with referenced z score > 2, or arrhythmias [2]. Patients with/without cardiac abnormalities were compared.

Disease severity was graded as follows: mild MIS-C—no vasoactive support, mild/no respiratory support, and minimal organ injury; moderate MIS-C—significant oxygen supplementation (> 5 L/min or high-flow nasal cannula), minimal vasoactive support [vasoactive infusion score (VIS) ≤ 10], and mild/isolated organ injury; severe MIS-C—noninvasive/invasive ventilation support, VIS > = 10, moderate/severe organ injury (including moderate-to-severe ventricular dysfunction) [3]. Patients with/without severe disease were compared.

Data were reported as mean ± SD (if normally distributed) or median (IQR) and counts/percentages (categorical variables). Chi-square and student independent t-tests were used for comparison of categorical and continuous variables, respectively. Nonparametric variables between groups were compared using Mann–Whitney U test. Risk factors for cardiac involvement and severe MIS-C were independently identified using univariate analysis. Multivariate analysis was done using forward LR method. A p < 0.05 was considered significant. SPSS version 24 was used.

Results

From June 2020 to February 2021, 53 patients satisfied the WHO-MIS-C criteria. Five were excluded (positive dengue-NS1 antigen/IgM-ELISA). Eight (16.7%) had history of SARS-CoV-2 infection/contact. Forty-five (93.8%) had positive SARS-COVID-IgG antibodies. Thirty-eight patients (79.2%) were at/above 75th centile; 21 (55%) were > 90th centile of weight for age. Two had underlying chronic neurological problems, rest were healthy.

Fever (n = 48, 100%), gastrointestinal (n = 40, 83%), and mucocutaneous (n = 24, 50%) symptoms were common. Fever duration was 3–7 d in 28 (58.3%) and > 1 wk in 14 patients (29.2%). Unusual presentations were: status epilepticus (n = 2), bilateral lower limb weakness (n = 1), diabetic ketoacidosis (n = 1), hyperlipasemia (n = 1).

Seventeen patients had mild MIS-C, 8 had moderate, and 23 had severe MIS-C. Thirty-three (68.8%) patients required respiratory support. One patient required ECMO. Four patients required renal-replacement therapy (Table 1).

Thirty-eight patients (80.9%) received intravenous immunoglobulin (IVIG). A combination of steroids ± IVIG was used in 44 (91.7%) patients. No patient received interleukin-1–receptor antagonists.

Forty-five patients (93.8%) recovered and 3 died (6.4%). All 3 had shock (VIS: 40–140) and platelet count < 25000/µL at admission.

Cardiac abnormalities group (n = 30): Twenty-six patients (54.2%) had abnormal ECHO, while 4 (8.3%) had isolated raised NT-proBNP levels. Eleven (42.3%) had low ejection fraction and 10 (20.8%) had coronary aneurysms. Pericardial effusion and mitral regurgitation were seen in 6 patients (23%).

Patients with and without cardiac abnormalities had significant differences in NT-proBNP, procalcitonin, sodium, albumin, and incidence of thrombocytopenia (Table 1).

On univariate analysis, shock, hypoalbuminemia, hypotension, and thrombocytopenia were identified to be significant risk factors for cardiac involvement (Supplementary Tables S1 and S2). Multivariate analysis was inconclusive.

Severe MIS-C group (n = 23): Median age was higher (12 vs. 7 y; p = 0.034). Median NT-proBNP, incidence of thrombocytopenia, and hypoalbuminemia were significantly higher. No difference was seen in incidence of cardiac abnormalities in patients with severe and mild/moderate MIS-C (73.9% vs. 52%, p = 0.117).

On univariate analysis, significant risk factors for severe MIS-C were age > 9.5 y, shock, high NT-proBNP, thrombocytopenia, hypoalbuminemia, and high ferritin > 380.5 ng/mL (Supplementary Tables 1 and 2). NT-proBNP > 1286.5 pg/mL [OR (95% CI): 24.92 (5.81–107.03), p = 0.001] and platelet count ≤ 119500/microliter [OR (95% CI): 21.59 (1.29–360.56), p = 0.032] were significant on multivariate analysis.

Discussion

The observations on the clinical presentation of MIS-C, in the present study, appear consistent with previous reports [4, 5]. Fever, gastrointestinal, and mucocutaneous symptoms were common. Epidemiological history was positive in less than 20% patients; hence, antibody screening is important in a suspected case.

Due to incomplete data on BMI, weight for age was used, which if > 75th and 90th centile identifies overweight and obese children, respectively [6]. A predominance of overweight children was observed. Obesity has been previously reported to be associated with MIS-C, especially severe disease [5].

Features of Kawasaki disease (KD) and MIS-C may have some overlap, but there are distinctions. While thrombocytosis is characteristic of KD, thrombocytopenia is seen in MIS-C. A high incidence of gastrointestinal symptoms (> 80%) was observed, which could be a clue favoring MIS-C in a patient with fever and/or KD-like symptoms. Older age is another
Table 1 Patients characteristics according to cardiac involvement and severity of the disease

|                          | Total (n=48) | Cardiac involvement | Severity | p value | p value |
|--------------------------|-------------|---------------------|----------|---------|---------|
|                          |             | Yes (n=30)          | No (n=18) |         |         |
| Age, median (IQR)        | 9.5 (4.5–13) | 9.5 (5–13)           | 9.5 (3–14) | 0.685   |         |
| Male, n (%)              | 30 (62.5%)  | 17 (56.7%)           | 13 (72.2%) | 0.281   |         |
| Age, gender adjusted    | 38 (79.2%)  | 24 (80%)             | 14 (77.8%) | 0.233   |         |
| weight > 75th centile, n | 102.9 ± 1.2 | 103.1 ± 1.2          | 102.6 ± 1.1 | 0.163   | 102.8 ± 1 |
| Mucocutaneous symptoms, n (%) | 24 (50.0%)  | 17 (56.7%)           | 7 (38.9%)  | 0.233   | 14 (56.0%) |
| Gastrointestinal symptoms, n (%) | 40 (83.3%)  | 25 (83.3%)           | 15 (83.3%) | 1.000   | 20 (80.0%) |
| PRISM, median (IQR)     | 9 (5–17)    | 9 (6–21)             | 7.5 (2–14) | 0.217   | 6 (2–9)  |
| Epidemiological history (previous positive COVID RT-PCR/contact history), n (%) | 8 (16.7%)  | 7 (23.3%)            | 1 (5.6%)   | 0.110   | 3 (12.0%) |
| Positive COVID antibody, n (%) | 45 (93.8%)  | 27 (90.0%)           | 18 (100.0%) | 0.166   | 24 (96.0%) |
| Highest WBC count, mean ± SD | 17650 ± 7601 | 17824 ± 7749.2       | 17361.7 ± 7560.5 | 0.84    | 15201.2 ± 6510.61 |
| Neutrophil lymphocyte ratio at admission, median (IQR) | 7.1 (3.8–12.4) | 6.2 (3.7–9.1)       | 10.7 (4.4–17) | 0.129   | 4.95 (2.8–8.2) |
| Thrombocytopenia, n (%)  | 24 (50.0%)  | 19 (63.3%)           | 5 (27.8%)  | 0.017*  | 8 (32.0%) |
| Thrombocytosis, n (%)    | 11 (22.9%)  | 7 (23.3%)            | 4 (22.2%)  | 0.029   | 8 (32.0%) |
| Lowest platelet count, median (IQR) | 117500 (79500–251500) | 100000 (76000–248000) | 167000 (85000–267000) | 0.407   | 231500 (89000–280000) |
| High procalcitonin, n (%) | 14 (29.2%)  | 13 (43.3%)           | 1 (5.6%)   | 0.005*  | 5 (20.0%) |
| High D-dimer, n (%)      | 36 (75%)    | 23 (76.7%)           | 13 (72.2%) | 0.231   | 15 (60.0%) |
| Ferritin ng/mL, median (IQR) | 381 (200–895) | 292 (186–915)       | 381 (224–875) | 0.745   | 258 (186–443) |
| NT-proBNP pg/mL, median (IQR) | 1060 (264–10800) | 5397.5 (867–18000) | 102 (55.3–987) | 0.001*  | 670 (93–1060) |
| CRP mg/L, median (IQR)   | 138 (35.7–244.3) | 145 (68–272)       | 75.4 (8.45–240) | 0.115   | 112 (48.9–210) |
| ESR, median (IQR)        | 46 (24–64.5) | 54 (9–69)            | 46 (46–46) | 0.843   | 46 (39–69) |
| Serum sodium meq/L, mean ± SD | 133.8 ± 4.2 | 132.7 ± 4            | 135.6 ± 4 | 0.019*  | 134.3 ± 3.66 |
| Serum albumin g/dL, mean ± SD | 2.8 ± 0.7    | 2.4 ± 0.6            | 3.1 ± 0.8 | 0.026*  | 3.1 ± 0.58 |
| Respiratory support, n (%) | Low-flow oxygen | 10 (20.8%)           | 8 (26.7%)  | 2 (11.1%) | 6 (24.0%) |
|                          | High-flow oxygen (including HFNC) | 9 (18.8%) | 6 (20.0%) | 3 (16.7%) | 4 (16.0%) |

*p < 0.05
distinguishing point. Similar to the present study, previous reports have also described higher median age in MIS-C (6–11 y) [3, 7].

Cardiac involvement is a prominent feature of MIS-C. The incidence of cardiac abnormalities in the present study was 54.2%, similar to other reports [2, 8]. Cardiac involvement was associated with vasoactive infusion requirement and thrombocytopenia, similar to a study by Pignatelli et al. [2].

It was observed that hypoalbuminemia, high NT-proBNP, and thrombocytopenia were common associations with cardiac involvement and severe MIS-C. Severity of thrombocytopenia correlated with disease severity. NT-proBNP > 1286.5 pg/mL predicted severe MIS-C. Both thrombocytopenia and high NT-proBNP appear to have an important role in early sick patient identification. Presence of such deranged parameters warrants intensive monitoring. This is relevant for triaging patients in resource-limited settings.

Interestingly, coronary aneurysms developed more in patients with mild/moderate MIS-C rather than severe disease. This is perhaps because the KD-like phenotype of MIS-C is less likely to have multiorgan involvement.

IVIG and steroids are the mainstay of treatment. Combination therapy is probably better than IVIG alone, as it improves recovery time and decreases complications [9, 10]. In the present cohort, steroids (alone/combined) were used more frequently than IVIG. High cost and limited availability lead to restricted IVIG use.

**Conclusion**

MIS-C is a possibility in any child with unexplained fever, even if epidemiological history is absent. Specific laboratory and cardiac evaluation establish early diagnosis. High NT-proBNP and thrombocytopenia predict severe disease.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s12098-022-04328-4.
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Declarations

Ethics Approval  The study was approved by the Medanta Institutional Ethics Committee and an MOU was duly signed by all the participating centers.

Conflict of Interest  None.

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