Clinical profile and outcome of cardiac manifestations in patients presenting with multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) can cause significant morbidity and mortality in children. This study was conducted to assess the pattern and outcome of cardiac abnormalities in MIS-C. This retrospective study was conducted in children with MIS-C between 1 month and 18 years. We enrolled 53 children with a mean age of 7.78 ± 4.62 years. Overall, 35.8% of children with MIS-C had cardiac manifestations in the form of coronary artery abnormalities (CAAs) or left ventricular (LV) dysfunction. Younger age (*P* 0.009) and high C-reactive protein at admission (*P* = 0.001) were significant predictors of cardiac involvement. CAAs were seen in 11.3% of children. On follow-up, 67% and 83% of children showed regression of CAA at 1 and 6 months, respectively. 24.5% of patients had presented with LV dysfunction. LV ejection fraction improved significantly at 1 month (*P* = 0.002) and 6 months (*P* = 0.001). Cardiac outcomes in MIS-C were favorable with timely identification and treatment.

Keywords: Cardiac outcome, coronary artery abnormalities, left ventricular dysfunction, multisystem inflammatory syndrome in children

INTRODUCTION

Since the recognition of coronavirus disease 2019 (COVID-19), it was realized that children, though relatively spared by the active infection with SARS-CoV-2, were more adversely affected by the autoimmune hyperinflammatory multisystem response to the same virus. This entity was termed multisystem inflammatory syndrome in children (MIS-C).[1] Cardiac manifestations of MIS-C form a key determinant that help distinguish MIS-C from severe acute COVID-19 and other infectious diseases. Therefore, it becomes essential to characterize the important cardiac manifestations of MIS-C.

Moreover, the existing literature on MIS-C seems to suggest that even though most patients recover from their illness, about 6%–14% of children have residual myocardial dysfunction at discharge, necessitating the need for long-term follow-up of these patients.[2] Hence, we undertook this retrospective study to assess the spectrum of cardiac manifestations and the outcome of cardiac abnormalities in our subset of children with MIS-C.

METHODS

We retrospectively evaluated children in the age group between 1 month and 18 years, admitted in the

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department of pediatrics, at our center from July 2020 to December 2021 with the diagnosis of MIS-C as per the World Health Organization Criteria.[3]

The demographic and clinical details of all children admitted with MIS-C were noted from their inpatient records. Children with cardiac manifestations of MIS-C were assessed in detail. The cardiac abnormalities detected at admission were compared with echocardiographic findings at 1-month and 6-month follow-up. Left ventricular ejection fraction (LVEF) was calculated using the Simpson's biplane method. Coronary artery diameters were assessed according to the standard criteria[4] and indexed with Z-scores.

Treatment protocol for multisystem inflammatory syndrome in children

The treatment protocol followed was based on the standard published guidelines/literature during the pandemic.[5] In general, patients received intravenous immunoglobulin (IVIG) 2 g/kg as a single-dose continuous infusion, with IV methylprednisolone 2 mg/kg/day as a first-line therapy. The dose of IV methylprednisolone was increased to 10–30 mg/kg/day in refractory cases.

Statistical analysis

Comparison of quantitative variables was done using the Paired *t*-test and Wilcoxon rank test for independent samples for parametric and nonparametric data, respectively. $P < 0.05$ was considered statistically significant. All statistical calculations were done using SPSS 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

RESULTS

Overall, 53 children were admitted with the diagnosis of MIS-C with a mean age of 7.78 ± 4.62 years and a male-to-female ratio of 5.6:1. The most common presenting symptom was fever, which was seen in 53 (100%) patients, followed by abdominal pain 21 (39%) and rash 15 (28%). 23 (43%) patients presented in shock, and among these, 13 (68%) patients had cardiac involvement.

Cardiac manifestations in MIS-C were seen in 19 (35.8%) children. These were in the form of LV dysfunction with or without valvular involvement and coronary artery dilatation. On univariate analysis, the important predictors of cardiac involvement in children were younger age ([mean: 5.61 years ± 4.17 SD], [$P = 0.009$]) and high C-reactive protein (CRP) at admission ([median: 186 mg/L and interquartile range: 25.5–248.4], [$P = 0.001$]). All 19 (100%) patients received steroids and 15 (78.9%) received IVIG. Of 19 patients of MIS-C with cardiac manifestations, 18 (94.7%) were successfully discharged and 1 (5.3%) died during hospitalization.

Six children (11.3%) were found to have coronary artery involvement [Figure 1]. Left anterior descending (LAD) was the most common artery involved (five of six patients). Both the patients with moderate and large aneurysms involve both left main coronary artery (LMCA) and LAD arteries [Figure 2].

At 1-month follow-up, regression of coronary artery dilatation was seen in four of six patients. The patients

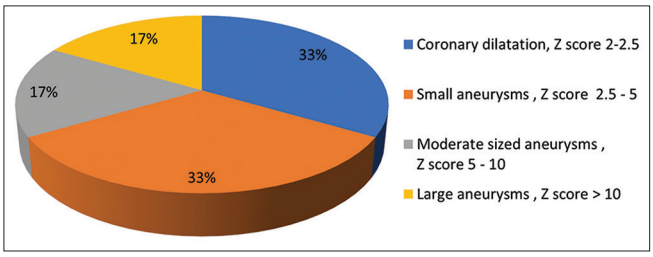

Figure 1: Coronary artery involvement

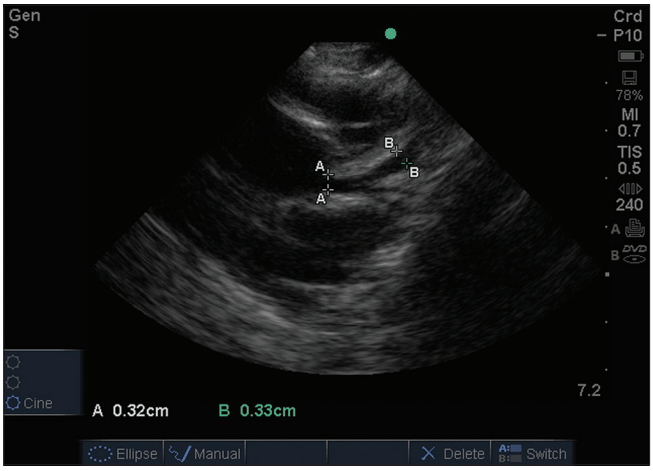

Figure 2: Coronary aneurysm of LMCA and LAD. LMCA: Left main coronary artery, LAD: Left anterior descending

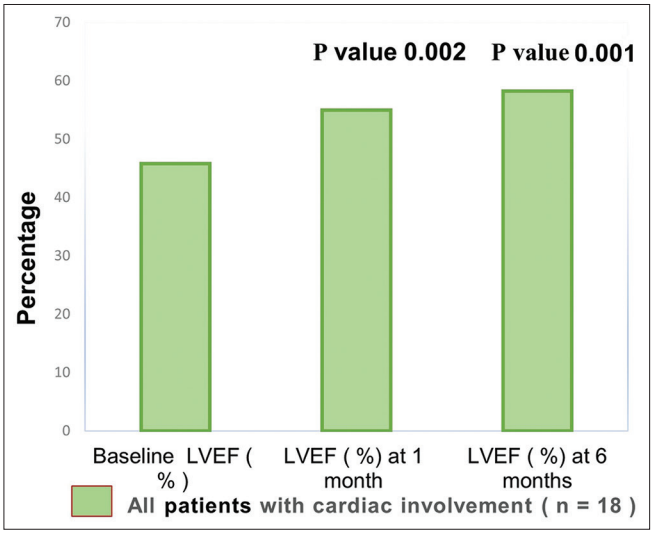

Figure 3: Comparison of pretreatment LVEF with LVEF at 1- and 6-month follow-up. LVEF: Left ventricular ejection fraction

with moderate and giant aneurysmal LAD had regression of LAD diameter with Z-score reducing from 6.99-3.9 to 11.6-8.7, respectively, with normalization of LMCA Z-score in both. The right coronary artery had normalized in all three patients at the end of 1 month. At 6-month follow-up, the coronary arteries had normalized in all, but one patient had mild LAD dilatation (Z-score = 2.4).

Of one-fourth (13/53) of the patients presented with LV dysfunction, 4 (7.5%) children also had associated mitral regurgitation. During follow-up, patients were screened with echocardiography for residual cardiac involvement at 1 and 6 months. The mean LVEF improved significantly after treatment on follow-up at 1 month and 6 months [Figure 3].

DISCUSSION

About one-third of children with MIS-C developed cardiac complications. Cardiac involvement was significantly higher in the younger age group and children with high C-reactive protein. The most common cardiac manifestation was LV systolic dysfunction, followed by coronary artery dilatation. Both cardiac manifestations showed significant recovery at 1 month and 6 months posttreatment.

In a study on cardiovascular involvement in MIS-C, Misra *et al.*[6] reported cardiac involvement in about one-third of patients with MIS-C, which is the same as the incidence reported by us. They reported the occurrence of shock in 52% of patients. However, other authors[7,8] observed shock in up to 77% of children with MIS-C. They also noted that 42% of patients had abnormal LVEF <55% at presentation. However, only one out of 54 patients had LVEF <55% at 10-week follow-up. Nonetheless, six patients had abnormal global LV longitudinal strain, demonstrating that the acute inflammation following MIS-C may leave behind subclinical residual myocardial damage in some patients, which is otherwise not observable in terms of reduced LVEF. These findings are in concordance with our study.

A systematic review showed that coronary artery abnormalities (CAAs) were seen in about 20% of children with MIS-C.[9] A multicentric study from 66 hospitals in the US[10] observed that coronary artery aneurysms were present in 13.4% of patients, quite similar to our reported incidence of 11.3%. Most of these patients (93%) had mild aneurysms that reverted to normal size in 79.1% of the patients by 30 days. Similarly, two-third of our patients with coronary involvement had small aneurysms, and 66% of children with CAA showed resolution of dilatation by 30 days.

Another important aspect which merits discussion is that MIS-C needs to be distinguished from Kawasaki disease (KD) since many clinical features show an overlap between the two entities. The data from our study as well as other studies[11] highlight the high prevalence of gastrointestinal symptoms and myocardial dysfunction in MIS-C, which are quite uncommon in classic KD. The presence of myocardial dysfunction is an important factor which helps distinguish MIS-C from KD as well as tropical fevers.

Overall, our study is in agreement with the existing literature with regard to the fact that cardiac involvement is common in MIS-C and timely institution of treatment leads to significant regression of these abnormalities.

Limitations

The limitations of our study are the retrospective nature of the study and the small sample size.

CONCLUSIONS

MIS-C is a potentially life-threatening condition. However, prompt recognition and appropriate management with immunosuppressive agents provide rewarding results. Younger age and high CRP at admission were found to be important predictors of cardiac involvement in MIS-C. LV systolic dysfunction and coronary artery dilatation showed significant resolution by 6 months posttreatment. Further, long-term studies with more sophisticated techniques may be needed to assess if any subtle residual cardiac abnormality continues to remain in the long term.

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Conflicts of interest

There are no conflicts of interest.

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