



Clinical Characteristics and Outcome of Multisystem inflammatory syndrome in Children in a Tertiary Care Center, Nepal

Puja Amatya¹, Rateena Rajbhandari², Sucharita Tuladhar², Sangita Basnet³, Anil Raj Ojha¹, Shrijana Shrestha³

¹Associate Professor, ²Assistant Professor, ³Professor

All from: Department of Paediatrics, Patan Academy of Health Sciences (PAHS), Patan Hospital, Lagankhel Rd, 44700, Lalitpur, Nepal.

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Abstract

Introduction: Multisystem inflammatory syndrome in children (MIS-C) manifests a few weeks after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is characterized by fever and multi-organ dysfunction. This disease has been increasingly reported from various countries since the outbreak of coronavirus in 2019. This study was done to determine the clinical characteristics and outcome of children with multisystem inflammatory syndrome in our settings.

Methods: This was a retrospective study in children aged one month to 14 years fulfilling the World Health Organization case definition of MIS-C conducted between January 2020 and March 2022 in a tertiary care center, Nepal. The clinical characteristics, treatment and outcome parameters of these patients were reviewed and analyzed.

Results: A total of 36 patients with MIS-C were reviewed. Among them, 20 (55.5%) were males and the median age was six years (IQR 1.6 - 10). All children with MIS-C had fever while gastrointestinal symptoms were present in 24 (66.6%), cough in 15 (41.7%) and rash in 13 (36%). Twelve patients (33.3%) had cardiac symptoms of which three (8%) patients had dilated coronary arteries. Other presentations were Kawasaki disease like features (8), toxic shock syndrome (5), meningoencephalitis (3), subconjunctival hemorrhage (1), and pulmonary edema (1). Intravenous immunoglobulin was given in 18 (50%) patients, steroid in 23 (64%) and aspirin in 30 (83.3%) patients. All patients survived.

Conclusion: The most common symptoms of multisystem inflammatory syndrome in children were fever, gastrointestinal symptoms, cough and rash. The overall outcome of patients even with severe disease was good.

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a condition characterized by fever, inflammation and dysfunction of multiple organs which manifests several weeks after the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ A cohort of eight children with MIS-C presenting with hyperinflammation and Kawasaki disease (KD) like features with a history of exposure to SARS-CoV-2 was first reported in United Kingdom in April 2020.² Similarly, there were case reports from Italy describing 10 children with MIS-C and 35 from France and Switzerland.^{3,4} As the international medical community gradually became familiar with this novel condition, hundreds of cases with fever, skin rash, conjunctivitis, oral mucosa changes, with minimal mortality started being reported since April

Correspondence

Puja Amatya,
Associate Professor,
Department of Paediatrics,
Patan Academy of Health Sciences (PAHS),
Patan Hospital, Lagankhel Rd, 44700,
Lalitpur,
Nepal.
Email: pujaamatya@pahs.edu.np



2020.^{5,6} The US Centres for Disease Control and Prevention formally named this condition MIS-C that is associated with coronavirus disease of 2019 (COVID-19), and introduced the case definition on May 14, 2020.⁷

In the year 2020, with the increase in COVID-19 cases in Nepal, Patan Hospital, a tertiary level teaching hospital situated in Lalitpur district, was designated "COVID dedicated hospital". Children started presenting to the hospital with KD and toxic shock syndrome (TSS) like features with multi-system involvement. Nepal reported the first death of a child with MIS-C on December 22, 2020. The first case of MIS-C diagnosed and managed at Patan Hospital was reported in July 2021.⁸ Children with COVID-19 infection or exposure to COVID-19 may present with MIS-C with overlap of KD like features. It can lead to diagnostic dilemma and challenges in management.⁹

There is paucity of data regarding clinical spectrum and outcome of MIS-C in Nepal. Hence, this study was planned to describe clinical characteristics and outcome of children with MIS-C in a low-resource setting to better aid in increasing the awareness of MIS-C among health care providers.

Methods

This is a retrospective study done at Patan Academy of Health Sciences (PAHS), Patan, Lalitpur, Nepal from January 2020 to March 2022 for a duration of 27 months. All children aged one month to 14 years fulfilling WHO case definition of MIS-C were eligible for this study.¹⁰ Diagnostic criteria for MIS-C with KD and TSS were defined by Verdoni et al and Center for Disease Control and Prevention respectively.^{3,11} The mild, moderate, and severe manifestations of MIS-C were classified. Mild manifestation was defined as patients having one or more of symptoms like fever, cough, diarrhea or rash without moderate and severe manifestations. Moderate manifestation was defined as patients having one or more of features like respiratory distress requiring oxygen, features of KD, features of acute kidney injury, acute hepatic injury or coagulopathy. Severe manifestation was defined as patients having one or more of the features like signs of shock, cardiac dysfunction, arrhythmias or depressed mental status. Hospital records of all admitted patients was reviewed and cases with suspected MIS-C were identified. Children aged one month to 14 years of age fulfilling WHO case definition of MIS-C were eligible for enrollment. Approval for the study was received from the local institutional review board (IRC - PAHS Ref: drs2208191669). The demographic profiles like age and sex and clinical manifestations of all children enrolled were recorded in the predesigned proforma. The treatment received and the outcome measures like need for mechanical ventilation, need of intravenous immunoglobulin (IVIG), development of coronary dilatation and death were recorded. The outcome

measures among children with mild, moderate and severe manifestation of MIS-C were compared. Data analysis was performed using STATA 17. Continuous variables like age and weight were presented as median (IQR). Categorical values for clinical manifestations were analyzed by Chi-square test. The association between moderate and severe manifestation as mentioned above and outcome parameters of MIS-C was analyzed by Chi-square test. A p-value of < 0.05 was considered statistically significant.

Results

Total of 50 children were admitted with diagnosis of suspected MIS-C. Of these, 36 cases fulfilled the criteria of MIS-C. Medical record was not available for 14 cases. The median age of children was six years (IQR; 1.6 - 10) and 21 (58.3%) were male, with male and female ratio of 1.4:1. Fever was present in all 36 patients (100%) followed by gastrointestinal symptoms in 24 (66.7%), cough in 15 (41.7%) and rash in 13 (36.1%) (Table 1). More than half of the children (19 / 36; 52.8%) presented with symptoms of moderate disease (Table 2).

Table 1: Clinical characteristics of patients with MIS-C

Clinical manifestations	N (%)
Fever	36 (100%)
Gastrointestinal symptoms	24 (66.7%)
Cough	15 (41.7%)
Rash	13 (36.1%)
Respiratory distress requiring oxygen	11 (30.6%)
Kawasaki like features	8 (22.2%)
Acute hepatic injury	8 (22.2%)
Shock	5 (13.9%)
Coagulopathy	4 (11.1%)
Cardiac dysfunction	3 (8.3%)
Decreased sensorium	3 (8.3%)
Acute kidney injury	2 (5.6%)

Table 2: Severity of MIS-C patients

Severity	N (%)
Mild	8 (22.2%)
Moderate	19 (52.8%)
Severe	9 (25%)

Among symptoms of moderate disease, respiratory distress requiring oxygen was present in 11 (30.5%), KD like features and acute hepatic injury each in eight (22.2%) cases and coagulopathy in four (11%) cases. Cardiac symptoms were present in 12 (33.3%) patients (Table 3). In this study cohort,

two patients had acute kidney injury (AKI) and improved with conservative management. Three patients had neurological features, all having features of meningoencephalitis, along with lower motor neuron facial palsy in one, flaccid paralysis in one and delirium in one. One patient had subconjunctival hemorrhage. Of the nine patients with severe manifestations, shock was present in five patients. Of the total 36 children with MIS-C, both IVIG and steroid were administered in 11 (30.5%) patients, while 12 (33.3%) and six (16.6%) received steroid and IVIG only respectively. Thirty (83.3%) patients received aspirin. There was no mortality in this study cohort.

Table 3: Abnormal echocardiography findings of patients with MIS-C

Echocardiography findings	N (%)
Pericardial effusion	3 (8.3%)
Coronary artery dilatation	3 (8.3%)
Left ventricular dysfunction	3 (8.3%)
Mild mitral regurgitation	2 (5.5%)
Dilated left ventricle	1 (2.8%)
Mild tricuspid regurgitation	1 (2.8%)
Atrial septal defect	1 (2.8%)

Table 4: Comparison of severity of MIS-C patients with outcome measures

Outcome measures	Severity of disease			P value
	Mild	Moderate	Severe	
IVIG				
Yes	0	9	9	< 0.001
No	8	10	0	
CAD				
Yes	0	0	3	0.02
No	8	19	6	
MV				
IMV	0	0	1	0.03
NIV	0	0	2	
No MV	8	19	6	

The outcome measures assessed in this study showed that 18 / 36 (50%) received IVIG, 3 / 36 (8.3%) had coronary artery dilatation (CAD) and 3 / 36 (8.3%) required mechanical ventilation. These outcome measures were then compared between children with different severity of MIS-C. All children with severe (9) and nine children with moderate disease but none of the children with mild disease received IVIG ($p < 0.001$). Similarly, CAD was observed in 3 / 9 (33.3%) children with severe disease and none in children with mild or moderate

disease ($p = 0.02$). Three out of nine (33.3%) patients with severe disease required mechanical ventilation, two requiring non-invasive ventilation (NIV) and one requiring invasive mechanical ventilation (IMV) while none of the children with mild or moderate disease required mechanical ventilation ($p = 0.03$) Table 4.

Discussion

The clinical manifestation of MIS-C is diverse. Due to varied signs and symptoms, its diagnosis is challenging and misleading. In this cohort, 36 patients were enrolled with male preponderance. The median age of children with MIS-C in this study was six years (IQR 1.6 - 10; range seven months - 14 years) which is less compared to studies from other countries where the median age was between 8 - 10 years.¹²⁻¹⁴ The reason for these differences may be due to more exposure to coronavirus in younger children in our settings. Published studies revealed that MIS-C is more common in males (55.5 to 66%) similar to our study cohort.^{12,13,15}

Fever is reported as the most common symptom seen in 90.8 - 100% of cases and it was present in all children in our study.^{12,13,16} Gastrointestinal symptoms (66.7%) were the second common manifestations of MIS-C patients in our study which was similar to the study by Kwak et al and Panaro et al where it was 70 - 71%.^{17,18} Cardiac symptoms are also frequently reported in MIS-C, up to 66% and as high as 81% in published studies.^{16,19} But in our study cardiac symptoms was present only in 33.3% cases. According to the published review, 31 - 58% of patients with MIS-C had left ventricular dysfunction.²⁰ A study by Feldstein et al reported that depressed left ventricular ejection fraction was present in 34.2% in MIS-C.²¹ This was high compared to our findings as only in 8.3% of MIS-C patients showed cardiac dysfunction. The lower number of cardiac manifestations and cardiac dysfunction in our study could be due to the delay in performing echocardiography as during that time period we lacked paediatric echocardiography facility at our center and on those whom we managed to do echocardiography by transferring patients to another center was done only once. Hence, we could have missed initial as well as later echocardiographic findings which could have been present during the period of illness.

Published data has revealed that the incidence of AKI in paediatric patients is variable, ranging from five to 37% in intensive care unit requiring renal replacement therapy in 20 - 23%.^{22,23} In our study, only 5.5% had AKI which was less as compared to the study by Whittakar et al, Bouchard et al, and Restrepo et al where it was 20-23% respectively.^{12,22,23} The reason for this could be due to more severe cases like shock and comorbidities at their centers. Respiratory symptoms were reported in 39% - 41% children with MIS-C which was similar

to our study findings of 41.7%.^{16,19} Another study by LaRovere et al revealed that neurological features was present in up to 20% of patients and had features like irritability, meningismus and severe encephalopathy.²⁴ Different studies reported presence of neurological symptoms in children with MIS-C varying between 11 - 16%.^{25,26} These findings were high as compared to our cohort where neurological manifestations were present only in 8.3% of MIS-C patients. The reason for this could be due to higher number of patients with multi-organ involvement and severe disease at the time of presentation in their cohort.

In our cohort a smaller number of patients required mechanical ventilator (8.3%) which was in contrast to the study done by Kurniawan et al where it was as high as 78% and study by Jiang et al and Panaro et al revealed that 17.07% and 15% of MIS-C patients required mechanical ventilation respectively.^{13,15,18} The reason for the difference may be due to less severity of illness at our center and may be very sick ones in our setting could not reach the hospital due to lack of resources and poor transport system. In our study around 14% patients had shock which was less as compared to 37.2% in a study by Jiang et al.¹³ Inotropic support was required in 13.8% in our cohort compared to 40% and 18% in studies by Panaro et al and Hajiani et al respectively.^{18,27} KD like features was present in 22.2% in our cohort which was similar to 25.7% in a study by Rostami et al.²⁸

Jiang et al revealed that 69.5% of MIS-C patients received IVIG, 54.9% received steroids, 48% received anticoagulation.¹³ Similarly, a study by Rostami et al revealed that IVIG, steroids, antiplatelet medicines were given in 94.2%, 77.8%, 68.4% patients respectively.²⁸ Compared to these results in our cohort, IVIG, steroid and aspirin was used in 50%, 63.9% and 83.3% respectively. Comparing these results, numbers of patients receiving IVIG were low in our cohort as compared to Jiang et al and Rostami et al as majority of children admitted in our center were from low socioeconomic status and without health insurance so they were unable to afford IVIG.^{13,28}

Overall, the outcome of MIS-C patients was good in our study. Similar results were observed in the study done by Jiang et al and Hajiani et al where survival was observed in 95.2 % and 97% respectively.^{13,27} Study by Acevedo et al has revealed much higher mortality 9%.²⁹ The reason behind this may be due to longer duration of the disease prior to being admitted to the PICU, more cardiovascular complications, more need of mechanical ventilation support and more need of RRT in non-survivors in their study cohort.

Study by Guntulu et al revealed that presence of renal symptoms ($P < 0.001$), respiratory symptoms (0.045), neurological symptoms (0.017), severe cardiac impairment (0.005) and need of mechanical ventilation were significantly

more common in non-survivors.³⁰ In our cohort as all patients survived, we were not able to compare these parameters between survivors and non-survivors. However, use of IVIG ($P < 0.001$), presence of coronary arterial dilatation ($P = 0.02$) and requirement of mechanical ventilation ($p 0.03$) were observed to be significantly high among those with severe disease in our study cohort.

The main limitation of this study is that this is a retrospective single centered study with small sample size. So, these results cannot be generalized to the all MIS-C patients.

Conclusion

The most common symptoms of MIS-C in our study cohort were fever, gastrointestinal symptoms, cough and rash. Majority of the patients had symptoms of moderate disease. The requirement of IVIG, presence of coronary artery dilatation and use of mechanical ventilation were more frequently observed with severe disease. The overall outcome of MIS-C patients, including those with severe disease, receiving per protocol treatment at our hospital, was good.

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