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LEADING ARTICLE

Clinical Presentation and Outcome of Multisystem Inflammatory Syndrome in Children in Dhaka Shishu (Children) Hospital

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Abstract

Background: *The increasing trend in multisystem inflammatory syndrome in children (MIS-C) during Covid-19 pandemic is alarming. Understanding the clinical course and outcome will give the clinical and public health implications of this syndrome.*

Objectives: *This study was conducted to find out the clinical presentation, course of the disease and outcome of the children and adolescents of MIS-C.*

Methods: *This observational study was conducted in the department of Pediatric Nephrology, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh, from August 2020 to October 2020. Total 12 children of MIS-C diagnosed according to WHO diagnostic criteria of MIS-C were included after taking written informed consent from the parents. Mean, median and standard deviation were calculated for the continuous variables.*

Results: *The age ranged from 17 days to 13 years, 56% were male, 17% were positive for SARS-CoV-2 by RT-PCR and 4(33%) had history of the COVID-19 exposure. Organ-system involvement included bilateral pneumonia in 92%, myocarditis in 78%, swollen hands and feet in 67%, mucocutaneous involvement in 50%, diarrhea in 50%, musculoskeletal involvement in 50%, acute kidney injury (AKI) in 33% patients and acute pancreatitis in 25% patients. The median duration of hospitalization was 11 days and ICU stay was 5 days. Mean duration of fever was 8.66 days. Kawasaki's disease-like features were documented in 50% patients and 4 of them had elevated level of procalcitonin and troponin I. Markedly elevated C reactive protein (CRP), Ferritin and D dimer in all patients were present. All patients with cardiac involvement had left ventricular dysfunction and ejection fraction was as low as 38.5%. Coronary-artery dilatation was documented in 33%. About 67% received intensive care with oxygen support by low flow nasal cannula or face mask, 33% received vasoactive support and systemic glucocorticoid, 50% received intravenous immunoglobulin (IVIG) plus methyl prednisolone. Antiplatelet and anticoagulant therapy was given in 75% and 33% patients respectively. Out of 12 patients 2 died, the contributing cause of death included complications like hypotension, shock, myocarditis, coagulopathy and AKI.*

Conclusion*: MIS-C led to serious and life-threatening complications especially when there are cardiac involvement, hypotension and acute kidney injury.*

Keywords: *Multisystem inflammatory syndrome, children, Kawasaki like disease, COVID-19.*

Introduction

During this COVID-19 pandemic an alarming increase in children presenting with fever, hyper inflammation and multiorgan dysfunction frequently requiring intensive care have been observed.[1-3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections may result in multisystem inflammatory syndrome in children (MIS-C). The clinical presentation of MIS-C includes fever, severe illnes and the involvement of two or more organ systems, in combination with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection. Some features of MIS-C resemble Kawasaki disease, toxic shock syndrome, and secondary hemophagocytic lympho-histiocytosis/macrophage activation syndrome.[1] The

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illness resembles Kawasaki disease (KD), with coronary dilatation and aneurysms occurring in some children, the cardiovascular manifestations were typically on the severe end of the KD spectrum with cardiogenic shock a common presentation together with other features. However, few patients present without the cardiovascular manifestations with other similar extra cardiac features; shows prompt recovery compared to those with cardiac manifestations.[1] So we need to pay special emphasis on those who presents with severe symptoms and KD spectrum with cardiogenic shock a common presentation together with other features. Recently a new definition has been given by WHO that define a unique syndrome named multisystem inflammatory syndrome in children (MIS-C). The clinical presentation of MIS-C includes fever, severe illness and the involvement of two or more organ systems, in combination with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection. The relationship of MIS-C to SARS-CoV-2 infection suggests that the pathogenesis involves post-infectious immune dysregulation.[1,3] Patients with MIS-C should ideally be managed in a pediatric intensive care environment since rapid clinical deterioration may occur.[1] Specific immunomodulatory therapy depends on the clinical presentation. In this study we have evaluated the clinical and biochemical profiles of children with MIS-C and their outcome in a tertiary care children hospital.[1]

Materials and Methods

This observational study was conducted in the department of Pediatric Nephrology, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh, from August 2020 to October 2020. Total 12 children of MIS-C diagnosed according to WHO diagnostic criteria of MIS-C were included after taking written informed consent from the parents. The case definition included 5 criteria: serious illness leading to hospitalization, an age of less than 21 years, fever that lasted for at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement, and positive RT-PCR or exposure to persons with COVID-19 in the past month. Their detail history, demographic information, clinical characteristics, laboratory values, hospital course, treatment, and outcomes were evaluated. Patients were treated with supportive measures; vasoactive support, intra venous immunoglobulin (IVIG) and pulse methyl prednisolone were given when there were echocardiographically detected cardiac abnormalities; anti-platelet agent and anti-coagulant were given in patients with raised D dimer.

We defined values for tachycardia, tachypnea, hypotension, lymphopenia, neutropenia, and elevated levels of D dimer, ferritin (all during the first 24-72 hours of admission) on the basis of age standards. Clinical myocarditis was defined as cardiac dysfunction on echocardiography with an elevated troponin level; when troponin levels were not tested, clinical myocarditis was defined as cardiac dysfunction (defined as any ventricular dysfunction or hypokinesia or decreased contractility or ejection fraction). Coronary artery aneurysm was reported on the basis of echocardiographic findings.

Presenting signs and symptoms were classified as constitutional (fever temperature more than 100°F, or subjective fever with chills), cardiovascular (chest pain), gastrointestinal (abdominal pain, nausea, vomiting, or diarrhea), dermatologic (rash or swelling of fingers, hands, toes, or feet), mucocutaneous (conjunctival injection or mucosal changes), neurologic (headache, altered mental status, or confusion), lymphadenopathy, musculoskeletal (myalgia or arthralgia), upper respiratory (congestion or sore throat), or lower respiratory (cough, shortness of breath, or wheezing).

Patient's age was grouped into 3 categories: less than 1 year, 1 year to 5 year and >5 year. Mean, median and standard deviation were calculated for the continuous variables.

Results

Among 12 patients 6 is were male and 6 were female age ranged from 17 days to 13 years. Half of the patients presented with cardiac involvement (Table-I).

Table I
Characteristics of the Patients

	Overall n=12	With cardiac involvement n=6	Without cardiac involvement n=6
Gender			
Male	6	3	4
Female	6	3	2
Age			
<1 year	2	0	2
1 year to 5 year	3	1	2
>5 year	7	5	2
Range 17 days to 13 years			

Amongst 12 patients 2 were COVID-19 RT-PCR positive and rests were negative. One patient aged 9 year was hospitalized following a road traffic accident and 1 month following admission became COVID-19 +ve and developed features of MISC Another COVID-19 + ve patient of 7 year was obese and among the rest none had any coexisting conditions or chronic illnesses. History of COVID-19 exposure was found in 4 patients and all of them were >5 years of age. All of the study patients presented with fever, 92% (n=11) of the patients presented with respiratory symptoms, 58% (n=7) with chest pain and cardiovascular system involvement and 6 of them were older than 5 year, 50% (n=6) with gastrointestinal system involvement, 25% (n=3) with abdominal pain and biochemically confirmed acute pancreatitis, dermatological involvement in the form of rash was found in 5 patients, swollen hands and feet were noticed in majority of the patients 8(67%), mucocutaneous involvement in 6(50%) patients, renal involvement as acute kidney injury (AKI) in 4(33%) patients, musculoskeletal involvement in 6(50%). None of the study patients had lymphadenopathy and neurological symptoms (Table II).

Table II

Clinical characteristics of the patients according to age group

Characteristics	Overall n=12	<1 year n=2	1 year to 5 year n=3	>5 year to 13 year n=7
Positivity for COVID 19 RT-PCR	2 (17%)	0	0	2
Coexisting condition	2 (17%)			2
Any (Road traffic accident)				
Chronic disease				
Obesity				
COVID 19 exposure prior to the onset	4 (33%)	0	0	4
Fever	12 (100%)	2	3	7
Cardiovascular: Chest pain(myocarditis)	7 (58%)		1	6
KD or atypical KD	6 (50%)	0	1	5
Gastro intestinal: n= 6(50%)				
Abdominal pain	4	0	1	3
Nausea	5	1	1	3
Vomiting	5	1	1	3
Diarrhea	6	1	2	3
Acute Pancreatitis n=3(25%)	3	0	0	3
Dermatological n=8 (67%)				
Rash	5	0	1	4
Swollen hands or feet	8	0	2	6
Mucocutaneous n=6(50%)				
Conjunctivitis	5	0	1	4
Mucosal change	6	1	1	4
Respiratory n= 11(92%)				
Lower respiratory	11	2	3	6
Bilateral pneumonia	11	2	3	6
Cough	11	2	3	6
Shortness of breath, wheezing	11	2	3	6
Musculo skeletal n=6(50%)				
Muscle ache n=6	0	0	0	6
Joint pain n=2	0	0	0	2
Lymphadenopathy (n=0)	0	0	0	0
Neurological(n=0)				
Headache	0	0		0
Altered mental status or confusion	0	0		0

All ptients were tested for SARSCoV-2 RT PCR; 2 (20%) patients showed positive RT PCR for COVID-19. None underwent antibody serologic testing due to unavailability. Four (33%) of the patiens had COVID-19 like illness 6 weeks before MIS-C symptoms appeared. Amongst 12 patients 11 had tachycardia and tachypnea, 7 presented with hypotension, 11 had temperature >100°F, none had oxygen saturation below 95%. Median WBC was 14,400 per cubic millimeter, median lymphocyte was 23.5%, median neutrophil count was 69.5%, median platelet count was 2, 65,000/ cubic millimeter. Most patients (12) had marked elevation of 3 biomarkers: CRP, Ferritin and D dimer, 8 had hypo-albuminemia. Four of the 6 patients with cardiac involvement had elevated troponin I levels. Elevated procalcitonin level was also found in 4 of 6 MISC patients. Chest radiograph of 11 patients showed features of pneumonia with bilateral opacities and 5 had mild to moderate pleural effusion. Ultrasonography of abdomen showed hepato-splenomegaly in 5 patients and only hepatomegaly in 4 patients, ascites was evident in 4 patients (Table III).

Table III

Vital signs and laboratory values of the patients

Vitals & lab parameters	Overall	<1 year	1 year to 5 year	>5 year to 13 year
Tachycardia	11	2	2	7
Tachypnea	11	2	2	7
Hypotension	7	0	1	6
Temperature >100°F	11	1	3	7
Oxygen saturation <92%	0	0	0	0
Median WBC per cubic millimeter	14,400	—	—	—
Median Lymphocyte (%)	23.5	—	—	—
Median Neutrophil (%)	69.5	—	—	—
Median Monocyte (%)	6			
Median platelet per cubic millimeter	2,65,000	—	—	—
Elevated Troponin level (n=4)				
Not done =8	4	0	1	3
Elevated CRP(mg/L)(n=12)		109±65	114.63±111.11	203.38±134.65
5-100	2	0	1	1
>100 to 200	4	2	1	1
>200 to 350	6	0	1	5
Elevated Ferritin level (ng/ml)(Mean ±SD, n=12)		1467±264.45	4008.33±6087.35	2763.14±3312.05
300-1000	5	0	2	3
>1000-5000	4	2	0	2
>5000	3	0	1	2
Elevated Procalcitonin level (ng/ml) (n=6)				
Done 6 (elevated n=4)Not done 6	4		1	3
Elevated D dimer (ng/L) (Mean±SD, n=12)		5.4±6.5	5.7±3.74	6.52±4.27
Elevated	10	1	3	6
Normal	2	1	0	1
Serum albumin level				
Low (<25 g/L)	8	1	2	5
Normal	4	1	1	2
Elevated level of SGPT n=2	2	1	0	1
Elevated Lipase n=3	3	0	0	3
Chest radiograph				
Bilateral opacities.	11	2	3	6
Mild to moderate pleural effusion	5	0	0	5
Ultrasonography of abdomen				
Hepatomegaly-splenomegaly	5	1	1	3
Hepatomegaly	4	0	1	3
Ascites	4	0	1	3

Left ventricular dysfunction was found in 6/12 (50%) patients with ejection fraction as low as 38.5% (Table IV). Coronary-artery dilatation was documented in 3 patients (33%) and brightness of coronary arteries in 2 patients, severe pulmonary hypertension (PHTN) in 5 patients and mild PHTN in 1 patient. Kawasaki's disease like features were documented in 6 (50%) patients. But none had lymphadenopathy or typical mucocutaneous features meeting the criteria for complete Kawasaki disease (Table IV).

The median duration of hospitalization was 7.75 days (range, 3 to 30 days). Mean duration of fever was 8.66 days; range 3 days to 30 days. Amongst 12 patients, 8 received intensive care (67%) and oxygen support by low flow nasal cannula or face masks but none of the surviving patients needed high flow oxygen or mechanical ventilation, 4 (33%) received vasoactive support,4 received methyl prednisolone only, 6 received IVIG plus methyl prednisolone. Nine (75%) patients received antiplatelet therapy and 4 patients received anticoagulant therapy. One patient received hemodialysis (Table V).

Table IV
Echocardiographic findings and KD like features

S/L	Age in year	Gender	Ejection fraction (EF %)	LV dysfunction	Coronary artery dilatation	Pulmonary hypertension	KD like features
1	13	M	40	yes	Brightness of coronaries	Severe PPHN	yes
2	9	F	45	yes	Perivascular brightness of right coronary artery with pericardial effusion	Severe PPHN	yes
3	9	M	38.64	yes	No coronary dilatation	Severe PPHN	yes
4	7	F	43	yes	Coronary artery dilatation	Severe PPHN	yes
5	9	F	44	yes	Left coronary artery dilatation	Severe PPHN	yes
6	3 1/2	F	55	yes	Dilated coronaries, with perivascular brightness	Mild PPHN	yes

Table V
Clinical course and treatment

Clinical course	
Mean duration of fever	8.66 days (Range 3 days to 30 days)
Median time from symptom of onset to hospitalization (days)	7.75 days (Range: 3 days to 30 days)
Mean duration of ICU stay (n=7)	4.8 days (Range 32 days to7 days)
Median time to ICU entry days	10 days (Range 32 days to 33 days)
Median length of hospital stay	11 days (Range 37 days to 30 days)
Therapy	
Oxygen support through low flow nasal cannula	8(67%)
Vasoactive support Inj. Dopamin+ Dobutamin	4(33%)
Systemic glucocorticoid	4(33%)
Systemic glucocorticoid + IVIG	6(50%)
Anti-platelet therapy	9(75%)
Anticoagulant therapy	4(33%)
Dialysis	1(8 %)

Table VI
Complications and outcome according to age groups

	Overall (n=12)	< 1 year	1-5 year	>5 year
KD or atypical KD	6	0	1	5
Myocarditis	7	0	1	6
Shock	1	0	0	1
Hypotension	1	0	0	1
Coronary artery dilatation	5	0	0	5
Acute kidney injury	4	0	0	4
Pancreatitis	3	0	0	3
Death	2	0	0	2

Most of the children older than 5 years developed life threatening complications; KD or atypical KD was found in 5 children older than 5 years and in only 1 child aged 3 and half year. Myocarditis was seen in 7 children and 1 of them presented with hypotension and another 1 with shock. Four patients presented with AKI amongst them 3 improved with supportive treatment, but 1 needed hemodialysis (HD). Out of the 12 patients 2 (17%) died, both had coronary artery dilatation. One had hypotension and another had shock, both of them had hyponatremia and AKI, one needed hemodialysis (HD) support. Three patients older than 5 years had abdominal pain and markedly elevated serum lipase with hyperglycemia and subsequently being improved. Out of 12, 10 patients were discharged with normal level of inflammatory markers with low dose oral corticosteroids for the next 6 weeks and was kept under regular follow up. On follow up all the patients showed normal echocardiographic findings during the next 2 months following discharge along with normal level of inflammatory laboratory markers (Table VI).

Discussion

As in previous studies in New York[2] and Italy[4], MIS-C cases in this series in Bangladesh followed the peak of the COVID-19 pandemic (August 2020 to October 2020) which supports geographic association between COVID-19 and MISC. Amongst 12 patients with MIS-C, 50 % were male, similar male preponderance (54%) was observed by previous authors.[2] In our series' we did not get patients older than 13 years of age, most of the patients (58%) were in between 5 to 13 years of age, which was comparable to 42% in New York study.[2] A neonate in this series was diagnosed as MIS-C, the presenting features were high fever, bilateral pneumonia and markedly raised inflammatory markers with normal echocardiography, sterile blood and urine cultures and negative RT-PCR for COVID-19 in both baby and mother. MIS-C in newborn although rare, but suspected case has been reported by previous authors.[2] In this study 2 (20%) patients showed positive RT-PCR for COVID-19, none underwent antibody serologic testing due to lack of facilities. Four patients (33%) had COVID-19 like illness 6 weeks before MIS-C symptoms appeared. Majority of the children and adolescents of New York report were COVID-19 positive[2] compared to only 2 patients (17%) in our cohort, which is much lower than other MIS-C studies.[1-3,5-12] It is possible that the seronegative patients in this cohort were either never infected with SARS-CoV-2 or their antibodies declined rapidly following mild or asymptomatic infections, similar possibilities has also been suspected in previous studies.[1,13]

Of the 12 patients in this series no one was admitted with a preexisting condition, only 1 had history of recent road traffic accident and was admitted for surgery and subsequently became COVID-19 positive. All the patients had fever at admission. The prevalence of respiratory symptoms was highest (92%), followed by cardiovascular, dermatologic, gastrointestinal, renal. We found variations in presenting symptoms and manifestations according to age. The prevalence of myocarditis (5/6), musculoskeletal symptoms (67%), AKI (33%) and acute pancreatitis (25%) was highest amongst

children older than 5 years of age. All the patients (12) underwent chest radiograph and[11] had features of bilateral pneumonia, severe clinical presentation was marked in patients with all age groups. Ultrasonography of abdomen showed hepatosplenomegaly in 5 patients and only hepatomegaly in 4 patients, ascites were evident in 4 patients. Overall, the clinical features of our cohort are comparable to those previously reported in the MIS-C literature.[2, 5-12,14,15]

A total of 6 patients presented with Kawasaki disease like symptoms with cardiac manifestations and most of them (5) were older than 5 years of age and echocardiogram of all of them had variable degrees of left ventricular dysfunction with ejection fraction as low as 38.5%. Coronary-artery dilatation was documented in 3 patients (50%) and brightness of coronary arteries in 2 patients (33%), severe pulmonary hypertension (PHTN) in 5 patients (83%). Of these 6 patients elevated level of troponin I was seen in 4(67%). Kawasaki disease like features with MIS-C has recently been described in New York and in few other countries but little in Northeast Asian countries, such as Japan, despite the prevalence of SARS-CoV-2 in this region.[15, 16] The median age of our cohort which was comparable to the median ages reported previously in the MIS-C literature[7,9,11] was considerably older than that of Kawasaki disease, where the peak incidence is 1-3 years of age.[16-19]

Death occurred in two children one aged 7 year and another was 9 year old both were female and presented with hypotension, shock and AKI. Both were admitted with abdominal pain and fever, had tachycardia and hypotension on presentation, and during the course of their hospitalization received vasopressor support and underwent intubation; one received IVIG, HD, another could not afford IVIG, but both received systemic glucocorticoids and vasoactive supports. The contributing cause of death for both children included complications like hypotension, shock, myocarditis, coagulopathy and AKI.

In addition, our MIS-C cohort appears clinically distinct from Kawasaki disease, none of our patients within our MIS-C cohort meeting the criteria for complete Kawasaki disease. Gastrointestinal symptoms and myocardial dysfunction are uncommon in Kawasaki disease, both of which were more prevalent in our MIS-C cases with cardiac involvement. The acute phase was characterized by increased levels CRP and ferritin (Table III), confirming acute inflammation. Raised troponin is indicative of myocardial dysfunction and injury.[12,15] Raised D-dimer in the acute phase suggests a procoagulant state. Although acute inflammation is common in Kawasaki disease, the procoagulant state seen in MIS-C patients is not a common feature of Kawasaki disease.[3,16-19] Immunologically, our MIS-C cohort appears distinct from Kawasaki disease as we did not observe neutrophilia and raised monocyte counts, which are features of Kawasaki disease, which is consistent with previous study reported by Carter MJ et al[3]. Amongst 12 patients, 67% needed ICU support but only 2 death cases needed mechanical ventilation. Complete recovery has been observed in 83% cases. In this study, patients were commonly treated with IVIG, glucocorticoids, and vasopressors. This constellation suggests an inflammatory vasculopathy with some similarities to Kawasaki disease. Our findings are consistent with those of other studies.[2,4,5] Previous investigators have also been suggested that patients with MIS-C should ideally be managed in a pediatric intensive care environment since rapid clinical deterioration may occur. Specific immuno-modulatory therapy depends on the clinical presentation. The relationship between the immune response to SARS-CoV-2 vaccines in development and MIS-C requires further study.[1-3]

Conclusion

Multiorgan dysfunction and systemic inflammation was clearly evident with MISC in children and appears distinct from Kawasaki disease. Multi-system inflammatory syndrome in children led to serious and life-threatening complications especially when there is cardiac involvement, hypotension and acute kidney injury. Patients with MIS-C should ideally be managed in a pediatric intensive care environment since rapid clinical deterioration may occur.

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