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SHORT TO MID TERM FOLLOW UP OF MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN(MISC) PATIENTS WITH CARDIAC INVOLVEMENT IN A TERTIARY CARE HOSPITAL IN RURAL BENGAL.

Paediatric Medicine

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ABSTRACT

Background & Objectives: Since mid-April 2020,clusters of paediatric cases of severe systemic hyper-inflammation and shock epidemiologically linked with COVID-19 were reported.WHO identified these cases as a novel condition named multisystem inflammatory syndrome in children (MIS-C). Many children with MIS-C have cardiological dysfunction like left ventricular dysfunction, pericardial effusion,coronary artery abnormalities viz.increased perivascular brightness,loss of tapering of coronary arteries,dilatation of coronary artery and aneurysm.Here we aim to describe the short to mid term follow up study of post-covid cardiac complications in MIS-C patients. **Methods:** This is a descriptive non-interventional study done in dept of paediatrics, Malda Medical college from august'21 to April'22. Detailed clinical examination was done in all MISC patients and only those who had cardiac involvement based on clinical and/or Echocardiographic finding were included in the study.The children underwent echo-cardiography during admission, 1months and 6months.Data was recorded and analysed. **Results:** In our study we have followed up these patients with repeat echocardiography at 1& 6 months and found out that initially 19.28% had coronary artery dilatation and 7.58% had small aneurysm.At 1month follow up,4.28% had dilatation and 1.42% had small aneurysm.At 6months follow up,1.4% had dilatation and none had aneurysm.LMCA(LEFT MAIN CORONARY ARTERY) was most commonly involved artery with 48.5% having dilatation and 22.8% having small aneurysm.This was followed by RCA(Right coronary artery)[dilatation:17.14% and small aneurysm:5.71%]and LAD(Left Anterior Descending)[dilatation:8.5% and small aneurysm:2.8%].LCX(Left Circumplex artery) was least involved [dilatation:2.8% and no aneurysm].None of the arteries had medium or giant aneurysm. **Interpretation & Conclusion:** Overall the prognosis is good with near- complete recovery at 6 months follow up. Limitation of the study is that this is a single centre study and we need multi centric study to build a stronger concensus with larger number of patients.These patients need to be followed up for long term (1year or more) as there are instances of late appearance of aneurysms.

KEYWORDS

multisystem inflammatory syndrome in children(MISC),follow up study,cardiac involvement,rural Bengal

INTRODUCTION:

Initial reports during the early phase of the COVID-19 pandemic indicated that children were relatively spared from severe manifestations, with 2–6% of children presenting with severe illness [1-3].However,since mid-April 2020,clusters of paediatric cases of severe systemic hyper-inflammation and shock epidemiologically linked with COVID-19 were reported.Riphagen et al. first described a case series of 8 previously asymptomatic children presenting with hyper-inflammatory shock, ventricular dysfunction, and multi-organ involvement [4].

This was followed by other reports of patients with Kawasaki disease (KD) and KD-like syndrome, frequently complicated by significant cardiac involvement [5-7].The World Health Organization (WHO) identified these cases as a novel condition named multisystem inflammatory syndrome in children (MIS-C), also called pediatric multisystem inflammatory syndrome (PMIC) [8].

Many children with MIS-C have cardiological dysfunction diagnosed on echocardiography like left ventricular dysfunction, pericardial effusion, coronary artery abnormalities viz. increased perivascular brightness, loss of tapering of coronary arteries, dilatation of coronary artery and aneurysm.Here we aim to describe the short to mid term follow up study of post-covid cardiac complications in MIS-C patients.

Definition of MIS-C

The WHO's definitions of the novel syndrome are shown in Table 1 [8].

Clinical presentation

Clinical symptoms

Children with MIS-C commonly present with persistent fever, diffuse erythematous polymorphic rash, non-purulent conjunctivitis, asthenia and prominent gastrointestinal symptoms [4-7].Other commonly reported symptoms are mucosal changes and peripheral edema, which, along with the rash and conjunctivitis, resemble the clinical characteristics of KD [5-7].Notably, a subset of patients presents with hypotension and shock from either acute myocardial involvement or systemic hyperinflammation/vasodilation, frequently requiring intensive care admission, circulatory, and respiratory support [4,5,6,7,9]

Laboratory findings

Elevated inflammatory markers and evidence of hyperinflammation were widely reported and consistently found in patients with MIS-C [4-7].C-reactive protein (CRP), procalcitonin (PCT), and erythrocyte sedimentation rate (ESR) are highly elevated, as well as ferritin and IL-6.D-dimer and fibrinogen are significantly increased. Leukocytosis, neutrophilia, lymphopenia, normal or decreased red blood cell count & platelet count are frequently seen.

Cardiac involvement

Myocardial dysfunction

Left ventricular (LV) systolic dysfunction has been commonly described in children diagnosed with MIS-C in both the initial reports and subsequent case series.The variable timing and modality of presentation with ventricular dysfunction suggests that different pathophysiological mechanisms may be responsible:while the acute infection may explain the occurrence of acute myocardial damage, a second phase characterized by a post-viral immunological reaction and systemic hyperinflammation may explain the occurrence of myocardial inflammation and dysfunction in predisposed subjects.In this second phase, a combination of cardiogenic and distributive shock may be observed.

Coronary involvement:

Coronary artery dilation or aneurysms have been described in 6–24% of patients.[4,5,10-20]. Most cases described mild coronary artery dilation with z-scores 2– 2.5.As coronary artery z-scores are based on healthy, nonfebrile children, some of the findings in the acute phase may be related to coronary vasodilation in the setting of fever and inflammation. However, there have also been reports of large and giant coronary artery aneurysms [4,15],and progression of coronary aneurysm following discharge raising concerns for coronary artery intimal disruption[4,5,14,15].The late development of coronary artery aneurysm highlights the need for ongoing follow-up of those patients.

Arrhythmia

Studies focusing on arrhythmic manifestations have described 7–60% of patients having rhythm abnormalities of variable.

Table 1: Case definitions for SARS-CoV-2-associated multisystem inflammatory syndrome in children

World Health Organization (WHO)
Children and adolescents 0–19 years of age with fever ≥3 days; AND two of the following: 1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet). 2. Hypotension or shock. 3. Features of myocardial dysfunction,pericarditis, valvulitis, or coronary abnormalities (including echo findings or elevated troponin/NT-proBNP), 4. Evidence of coagulopathy (by PT, PTT, elevated d-dimers). 5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain). AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19. Consider this syndrome in children with features of typical or atypical KD or toxic shock syndrome

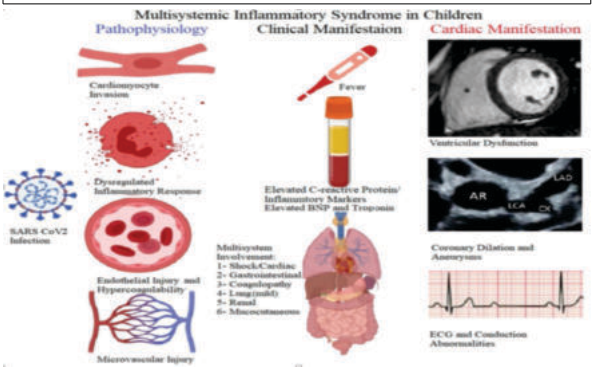

Figure 1. Summary of the potential causes, clinical presentation, and cardiac manifestations in multisystem inflammatory syndrome in children. [22]

MATERIALS AND METHODS:

METHODS:

This is a descriptive non-interventional study done in dept of paediatrics ,Malda Medical college from august'21 to April'22.All the patients admitted in the department were diagnosed as MISC based on WHO criteria. Detailed clinical examination was done in all MISC patients and only those who had cardiac involvement based on clinical and/or Echocardiographic finding were included in the study. The children underwent echo-cardiography during admission, 1months and 6months.

SAMPLING:

Convenient sampling technique was adopted as this is new study with very little literature review and all the patients during the study period who fulfilled the inclusion criteria were included in the study.74 children were included in the study.

Inclusion Criteria:

All the children (age group 1month to 12years) who fulfilled the WHO criteria for MISC and had cardiac involvement either clinical and/or echocardiographic involvement were included in the study.

Exclusion Criteria:

Those who had previous congenital or rheumatic cardiac disease were excluded. Data was recorded in case record form and put on Microsoft excel sheet and analysed.

RESULTS :

74 children were included in the study and 4 were lost to follow up.Among the 70 children who were finally analysed for our study, 42 were male (60%) and 28(40%) were female.Age of the cases ranged from 2 month to 11 yrs10 months with mean being 3yr10months.All patients presented with fever (100%).Gastrointestinal symptoms including vomiting (84.2%),diarrhoea (85.7%),and abdominal pain (74.2%) are common.Respiratory symptoms are seen in 54.2%.Neurological symptoms comprise headache (51.4%),altered sensorium (28.5%), GTCS (11.4%).Shock was seen in 65.7% patients.Rash was seen in 60% patients while mucocutaneous inflammation was seen in 50%.[table 2] Pallor(80%), hepatomegaly(31.4%), spleenomegaly(24.3%), jaundice(15.7%), ascites (25.7%) were the most common signs noted in these children.[table 2]

On initial echocardiography 28(46%) had diminished left ventricular function.27(38.5%) had altered ECG findings (arrhythmia, nonspecific ST, T wave changes, prolonged PR and QT intervals).Based on the criteria of 1)Dilation of coronary artery:z score 2 to 2.5, 2)small aneurysm: z score 2.5 to 5, 3)medium aneurysm: z score 5 to 10, and 4)giant aneurysm:z score >10 or diameter >8 mm,there was overall 19.28 % dilatation of coronary arteries and 7.58 % had small aneurysm. When individual coronary artery were considered, 12(17.14%) RCA showed dilatation [mean Z score 2.21]and 4(5.71%) RCA had small aneurysm[mean Z Score 2.83]. Similarly 6(8.5%) LAD showed dilatation[mean Z Score 2.12] and 2 (2.8%)LAD had small aneurysm[mean Z Score 3.12],34(48.5%)LMCA showed dilatation[mean Z Score 2.09] and 16(22.8%)LMCA had small aneurysm[mean Z Score 3.41], 2(2.8%) LCX had dilatation[mean Z Score 2.03] and no LCX had aneurysm. [table 3]

Table 2: Clinical Manifestations And Demographic Data Of Misc Patients Included In The Present Study:

Clinical manifestations	N(70)	%(100)	Demographic data	N	%
Fever	70	100	Age		
Vomiting	59	84.2	1mnth-2yr	30	42.8
Abdominal pain	52	74.2	2-8yrs	20	28.5
Diarrhoea	60	85.7	9-12yrs	20	28.5
Conjunctivitis	24	34.2			
Mucocutaneous inflammation	35	50	Gender		
Oedema	48	68.5	Male	42	60
Rash	42	60	Female	28	40
GTCS	8	11.4			
Headache	36	51.4			
Altered sensorium	20	28.5			
Shock/hypotension	46	65.7			
Respiratory symptoms	38	54.2			
Hepatomegaly	22	31.4			
Splenomegaly	17	24.3			
Jaundice	11	15.7			
Pallor	56	80			
Ascites	18	25.7			

Table 3: Comparison Of Different Coronary Artery Dilatations(z Score)at Time Of Admission ,after 1month And 6months:

CORONARY ARTERY DILATATION	(Z –SCORE)	At admission(0)		After 1months		After 6months	
RCA(RIGHT CORONARY ARTERY)		N(70)	Mean Z score	N(70)	Mean Z score	N(70)	Mean Z score
	<2	54	0.51	68	0.45	68	0.49
	2-2.5	12	2.21	2	2	2	2
	2.5-5	4	2.83	0		0	0
	5-10	0	0	0		0	0
LAD(LEFT ANTERIOR DESCENDING ARTERY)		N(70)	Mean Z score	N(70)	Mean Z score	N(70)	Mean Z score
	<2	62	0.83	68	0.82	70	0.82
	2-2.5	6	2.12	2	2.3	0	0
	2.5-5	2	3.12	0	0	0	0
	5-10	0	0	0	0	0	0
LMCA(LEFT MAIN CORONARY ARTERY)		N(70)	Mean Z score	N(70)	Mean Z score	N(70)	Mean Z score
	<2	20	1.26	58	1.09	70	1.12

	2-2.5	34	2.09	8	2.08	0	0
	2.5-5	16	3.41	4	2.58	0	0
	5-10	0	0	0	0	0	0
LCX(LEFT CIRCUMFLEX ARTERY)		N(70)	Mean Z score	N(70)	Mean Z score	N(70)	Mean Z score
	<2	68	1.4	70	0.62	70	0.31
	2-2.5	2	2.03	0	0	0	0
	2.5-5	0	0	0	0	0	0
	5-10	0	0	0	0	0	0

DISCUSSION:

Acute myocardial dysfunction is the most common cardiac finding in patients with MIS-C [25]. In the initial case series from the United Kingdom and Italy, 6 of 8 and 5 of 10 patients were reported to have left ventricular (LV) systolic dysfunction. Subsequent larger case series have reported depressed LV ejection fraction in ≈50% to 60%, with patients presenting in shock having the highest risk of LV dysfunction [15,21,25]. A recent study reported a series of 35 patients from 14 intensive care units in France and Switzerland with acute heart failure attributable to MIS-C , Coronary artery dilation and aneurysms have been described in MIS-C [15,19,20].The incidence of coronary artery abnormalities varies significantly among reports. Most of the larger series have reported coronary changes in 8% to 24% of patients[16]. Although the majority of patients demonstrated small aneurysms (Z score 2.5 to 5), there have been rare cases of large/ giant aneurysms (Z score ≥10) and aneurysms that developed later during the convalescent period[5,15]. The pathologic mechanism of coronary artery dilation/aneurysm in MIS-C has not been elucidated. Coronary dilation in MIS-C may be related to fever and circulating inflammatory mediators or may be attributable to inflammation and disruption of the arterial wall as is seen in KD. The percentage of patients with LV dysfunction and coronary artery involvement in the case series published to date is shown in table 4.

Despite extensive search, we found very few studies showing the short and midterm follow up of these MIS-C patients with cardiac involvement. In our study we have followed up these patients with repeat echocardiography at 1 and 6 months and found out that initially 19.28% had coronary artery dilatation and 7.58% had small aneurysm. At 1month follow up, 4.28% had coronary dilatation and 1.42% had small aneurysm. At 6months follow up, 1.4% had coronary dilatation and none had small aneurysm.

LMCA(LEFT MAIN CORONARY ARTERY) was most commonly involved artery with dilatation:48.5% and small aneurysm:22.8%. This was followed by RCA(Right coronary artery)[dilatation:17.14% and small aneurysm: 5.71%]and LAD(Left Anterior Descending)[dilatation:8.5% and small aneurysm:2.8%].LCX[Left Circumflex artery) was least involved [dilatation:2.8% and no aneurysm].

None of the arteries had medium or giant aneurysm in our study. Overall the prognosis is good with near complete recovery at 6 months follow up.

Limitation of the study is that this is a single centre follow up study and we need multi centric follow up study to build a stronger concensus with larger number of patients. These patients need to be followed up for long term (1year or more) as there are instances of late appearance of aneurysms..

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Conflict of interest: None

TABLE 4: The percentage of patients with LV dysfunction and coronary artery involvement in different case series :

Authors	Region of origin	N	Age,Y	Cardiac involvement	Coronary involvement	Arrhythmia/ECG changes
				Ventricular function		
Riphagen et al4	London,UK	8	Range,4 to 14	6/8 (4/8 Mild to severe LV dysfunction)	8/8 bright coronary vessels, 1/8 giant aneurysm	1/8 ecg change
Verdoni et al5	Bergamo, Italy	10	Mean 7.5 (SD 3.5)	5/10 LVEF <50%	2/10 Coronary aneurysms	--
Belhadjer et al[21]	France and Switzerland (14 centers)	35	Median 10 (range, 1 to 16)	35/35 LVEF <50% (inclusion criteria), 10/35 LVEF <30%, 31/35 global LV hypokinesis, 3/35 segmental wall hypokinesis,	6/35 Mild dilatation	1/35 ST elevation
Grimaud et al[12]	Paris, France (4 centers)	20	Median 10 (IQR, 3 to 15)	20/20 Cardiogenic/ vasoplegic shock, LVEF 35%	Normal coronary arteries	--
Toubiana et al[13]	Paris, France	21	Median 8 (range 4 to 17)	16/21 Myocardial injury	5/21 Moderately dilated coronary (z score 2 to 2.5), 3/21 bright coronaries	2/16 Increased QT interval
Whittaker et al[15]	UK (8 centers)	58	Median 9 (IQR, 6 to 14)	18/29 LV dysfunction	8/58 Coronary artery dilatation (z score >2), 7/58 z score>2.5, giant aneurysm 2/58	4/58: ECG changes
Cheung et al[14]	New York, United States	17	Median 8 (range, 2 to 16)	11/17 Normal to mild LV dysfunction; 6/17 moderate to severe LV dysfunction	7/17 Echo-bright coronaries, 1/17 medium-sized aneurysm (z score 5.2)	10/17 Nonspecific ST/T-wave abnormalities
Valverde et al[23]	Europe, 55 centers	286	Median 8.4 (IQR, 3.8 to 12.4)	52% Reduced ejection fraction, 9% with ejection fraction <40%	69/286 (24%) With dilation, 56 small aneurysms 15 moderate aneurysms 1 patient with giant aneurysm	Abnormal ECG in 25%,
Feldstein et al[20]	United States, 26 states	186	Median 8.3 (IQR, 3.3 to 12.5)	61 (33%) Ejection fraction 30% to 55%, 9 (5%) ejection fraction <30%	15/186 (8%) Aneurysm (z>2.5)	--
Dufort et al[19]	New York Department of Health	99	31% <5, 42% 6 to 12, 26% 13 to 20	52% Decreased ejection fraction	9 (9%) With aneurysm, 4 small aneurysms (2.5<z<5)	--
Kaushik et al[18]	New York, United States	33	Median 10 y (IQR, 6 to 13)	21/33 (66%) Depressed LV function, 4 (12%) with LVEF <30%	4/33 Had "prominent" coronaries and 2/33 had left main coronary ectasia	--
Our study	Malda, West bengal	70	Median3yr8m Range 2mnth to11yr10mnths	28/74(46%)depressed LV function,	Dilation-19.28% Small aneurysm—7.85% Medium aneurysm- nil Giant aneurysm- nil	38% had ecg changes

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