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Original Research Article

Kawasaki like illness in COVID versus Kawasaki disease in pre-COVID era

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ABSTRACT

Background: In children and adolescents, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is mostly responsible for mild respiratory symptoms, in contrast with severe forms reported in adults. An association between the disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19), and late manifestations of vasculitis has been increasingly suspected.
Method: All children and adolescents (aged ≤18 years) who were diagnosed with Kawasaki disease (KD) and KD shock syndrome (KDSS) as per AHA and Kanegaye et al criteria. From each patient we obtained at least two nasopharyngeal swabs to test for SARS-CoV-2 using reverse transcription- polymerase chain reaction (RT-PCR). We also took blood samples to test for IgG antibodies against SARS-CoV-2.
Results: Leucocytosis was found in majority with median leucocyte count of 10100 predominant neutrophila. Inflammatory markers D dimer, serum ferritin and fibrinogen level were raised. The 43% patients had coronary artery aneurysm. The 75% patient had some form of Left ventricular systolic dysfunction. All patients received IVIG while 13 patients received both IVIG and methyl predinisolone. Ionotropes were used in 68%. Two patients received tocluzumab.
Conclusions: In this study we found increased incidence of Kawasaki like illness temporally associated with COVID-19. Older age of presentation with more atypical presentation.

Keywords: KD, COVID-19, KDSS, IgG, RT-PCR

INTRODUCTION

Kawasaki disease (KD) is a medium vessel vasculitis of undetermined etiology usually affecting children below 5 years.[1] The first report of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emanated from Wuhan, China in November 2019. It then spread rapidly around world. In April 2020, Verdoni et al reported 30 times increase in incidence of KD from Bergamo, Italy since the onset of this pandemic.[2] Further, the authors also noted increased disease severity in patients with KD during this period. There has also been a noticeable increase in incidence of 'Kawasaki-like illness' in association with COVID-19) pandemic.[2-6] Confirmation of infection with COVID-19 in these reports has been through serology and/or RTPCR. Our study is aimed to find out clinical profile of KD in COVID-19 era and compare it with KD in pre COVID-19 era. Study is also aimed to find similarities and differences in KD in COVID-19 and pre COVID-19 era.

METHODS

After obtaining the ethical clearance from the institutional review board vide their order no. IRB/GMC/C3, the present hospital based prospective and retrospective study was conducted prospectively from October 2020 to April 2021.

Inclusion criteria

Children less than 18 years of age and children whose parents consented to participate were included in the study.

Exclusion criteria

Children greater than 18 years of age and children having chronic illness or any syndrome association were excluded.

All children less than 18 years of age were admitted in the department of paediatrics and neonatology, government medical college, Srinagar with the diagnosis of KD (AHA 2017) from October 2020 to April 2021.[7] For each patient we took complete clinical history and physical examination. Laboratory parameters included complete blood count, liver function tests, kidney function tests, electrolytes, inflammatory markers (D dimer, ferritin, fibrinogen), nasopharyngeal swab for SARS-Cov-2 RTPCR, IgG antibodies against COVID-19. Cardiac evaluation included 12 lead ECG, echocardiography, CT angio for coronaries. In retrospective (April 2017 to October 2019) we compared our results by looking retrospectively at medical records of patients admitted with KD in our hospital from April 2017 to October 2019 (AHA 2017 criteria for diagnosis).[7]

The recorded data was compiled and entered in a spreadsheet (Microsoft excel) and then exported to data editor of SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and pie diagrams. A $p<0.05$ was considered as statistically significant.

RESULTS

Table 1 shows age of presentation. In our study 21 patients got admitted during pre COVID era and 16 patients during COVID era. 18.5% of children in COVID 19 era were more than 9 years of age while none of the patient was more than 9 years in pre COVID 19 era. Relationship was significant for column proportion with $p<0.05$.

Table 1: Age distribution in study patients.

Age (Years)	Pre-COVID, (n=21)		COVID, (n=16)	
	N	%	N	%
<1	3	14.2	2	12.5
1-5	16	76.19	3	18.75
6-9	2	9.52	8	50
9-18	0	-	6	18.75

Table 2 shows clinical profile of patients both in COVID and pre COVID era. Fever was present in all patients in both COVID and pre COVID era. Patients in pre COVID era present with fever, conjunctivitis, rash and oral mucosal changes while in COVID era patients present with fever, gastrointestinal symptoms, hypotension and shock.

Table 2: Clinical symptoms in study patients.

Clinical symptom	Pre-COVID, (n=21)	COVID, (n=16)	P value
Fever	21	16	
Conjunctivitis	17	4	0.0006
Cervical lap	7	1	0.04
Extremity changes	13	2	0.002
Maculopapular rash	18	4	0.0001
Oral mucosal change	18	3	0.0001
GI symptoms	4	13	0.001
Arthralgia/ arthritis	6	Nil	
Hypotension/ shock	Nil	2	
Respiratory symptoms	Nil	1	

Table 3: Investigations.

Investigation	Pre-COVID, (n=21)	COVID, (n=16)
Hemoglobin (Median value)	10.6	10.1
TLC (Median value)	10100	9800
Neutrophilia (%)	17	11
Lymphocytosis (%)	3	5
Platelet count (Median value)	450000	165000
AST (Median value)	38	38.2
ALT (Median value)	42.5	34
Albumin (Median value)	3.01	3.5
CRP (Median value)	54	59
ESR (Median value)	49	47

Table 3 shows laboratory parameters in pre-COVID and COVID era. Laboratory parameter included leukocytosis with predominant neutrophilia was seen in both patients in pre-COVID and COVID KD. Remarkably thrombocytosis which was seen in pre-COVID-19 KD was less common in COVID KD. The median platelet count of 1,65000 was seen in COVID-19 era as compared to 4,50000 in pre-COVID-19 era and relationship was statistically significant. Additional investigations in COVID era were RTPCR for COVID which was negative in all patients, ANTI SARS antibodies positive in 14 patients. Inflammatory markers increased in COVID era were serum ferritin with median value of 614.5 ng/ml, D-dimer median value 4.6 ng/dl, Fibrinogen median value

460 mg/dl. Table 4 shows echocardiographic findings and treatment received. Coronary artery abnormality was seen both in COVID and pre-COVID era. In COVID era 12 patients present with left ventricular dysfunction while none of patients in pre-COVID era present with left ventricular dysfunction. Peri cardiac collection were seen in only 1 patient in COVID era as shown in Table 4 (A).

Table 4 (A): Scoring.

Variables		Pre-COVID, (n=21) (%)	COVID, (n=16) (%)
Z score	Normal <2	10 (47.6)	9 (56.2)
	Abnormal >2	11 (52.3)	7 (43.7)
Ectasia		2 (9.5)	4 (25)
Small		7 (33.3)	1 (6.25)
Medium		1 (4.7)	Nil
Large		1 (4.7)	2 (12.5)
LV dysfunction		Nil	12 (75)
Pericardiac collection		Nil	1 (6.25)

Table 4 (B): Treatment therapy used.

Treatment	Pre-COVID, (n=21) (%)	COVID, (n=16) (%)
Intravenous immunoglobulin	21 (100)	16 (100)
Methylprednisolone	2 (9.5)	13 (81.2)
Aspirin	21 (100)	16 (100)
Warfarin	1 (4.7)	2 (12.5)
Tocliuzumab	Nil	2 (12.5)
Ionotrops	Nil	11 (68.75)

Table 4 (B) shows treatment received in patients. Intravenous immunoglobulins were given in all patients both in COVID and pre-COVID era. In COVID era 13 patients were treated with steroids. Toclizumab was used in 2 patients in COVID era. 11 patients needed ionotropic support in COVID era.

DISCUSSION

The study was conducted in postgraduate department of pediatrics, govt medical college Srinagar. In this study 21 pre-COVID-19 patients from April 2017 to October 2019 were compared with 16 COVID-19 era patients between October 2020 to April 2021.

In our study those diagnosed in COVID-19 era demonstrated higher age of presentation, significant number of patients were adolescents or early adolescent age. The 18.5% of children in COVID-19 era were more than 9 years of age while none of the patient was more than 9 years in pre COVID-19 era. Higher age of presentation was noticed in study by Verdoni et al were mean age of presentation in COVID era was 7.5 years vs 3 years in pre-COVID era.[2]

Cardinal presenting symptoms of KD rash, conjunctivitis, lymphadenopathy, mucocutaneous changes were less commonly seen in COVID era KD and relationship was statistically significant. Gastrointestinal manifestations vomiting, abdominal pain and diarrhea were predominant symptoms in COVID-19 KD. Two patients with COVID-19 KD presented with profound hypotension and shock. Predominant gastrointestinal manifestations 80% with any gastrointestinal symptom, 60% with abdominal pain, 58% nausea and vomiting, 9% with diarrhea were reported in study by Panupattanapong et al.[8] Laboratory parameter included leukocytosis with predominant neutrophilia was seen in both patients in preCOVID and COVID KD. Remarkably thrombocytosis which was seen in pre-COVID-19 KD was less common in COVID KD. The median platelet count of 1,65,000 was seen in COVID 19 era as compared to 4,50000 in pre-COVID-19 era and relationship was statistically significant. Inflamatory markers CRP, ESR and transaminitis was seen in both the groups. In COVID era additional inflammatory markers, D dimer, serum fibrinogen, and serum ferritin were also elevated. All patients were negative for COVID-19 RTPCR and 14 out of 16 i.e., 87% were antibody positive.

In our study 52.3% and 43.75% children with pre-COVID KD and COVID KD respectively had abnormal coronary artery at diagnosis. Two patients with COVID KD have aneurysmally dilated coronary. In multicentric study by Ramacharan et al reported 93% of children with CAA.[9] The lower incidence of CAA in our study is that we followed AHA 2017 criteria for CAA[7] and mere prominence of coronary arteries was not considered abnormal.

Remarkably 75% of patient in COVID KD had some degree of myocardial dysfunction in echocardiography which was not seen in pre-COVID KD. Symptomatic myocarditis has been reported in 40-80% of patients in MIS-C.[10,11] In contrast symptomatic myocarditis is seen in <5% in pre-COVID KD.[12] There has been much debate regarding KD and cardiac findings in MISC and whether they are same or separate entities as cause of KD has yet to be identified but believed to be triggered by a preceding infection. There is much to learn from patients of KD in COVID era where SARS Cov 2 may trigger inflammatory cascade.

All patients of KD in COVID era and preCOVID era received intravenous immunoglobulin and aspirin as per AHA 2017 protocol.[7] American college of rheumatology published a task force recommendation for patients with KD like illness temporally associated with SARCov 2 infection in June 2020 and December 2020 in which glucocorticoids where recommended for KD illness in COVID. Glucocorticoids was used in 13 patients in KD in COVID era who presented with ill appearance,

unexplained tachycardia, shock and who required intravenous iontrops. Two cases with markedly elevated IL6 received toclizumab. Therapeutic anticouglation was used if giant coronary aneurysm (Z score >10) were seen AHA 2017. Intravenous iontrops were used in 11 out of 16 patients in COVID KD who had left ventricular dysfunction and shock. Intravenous iontrops was not used in any patient with pre-COVID KD as none had left ventricular dysfunction.

Special mention about two patients admitted with KDSS.[13] Both the patients were adolescent boys. They had severe LV dysfunction and aneursymally dilated coronaries on ECHO. CT angio was done to delineate coronary artery anatomy. Both these patients had iontrope refractory shock with markedly high IL6. Tocluzimab was given in these two patients following which there was clinical improvement.

CONCLUSION

Results from this study suggest that COVID-19 may be one of triggers of KD. KD in older patients with COVID-19 is associated with increased cardiac involvement, lower platelet count, and Kawasaki shock syndrome. Early treatment with steroid should be considered in the patient with COVID-19 KD.

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