

Original Research Article

Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 in Indian children: Pune experience

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ABSTRACT

Background: Aim was to study the clinical profile, laboratory parameters and outcome of children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).

Methods: This is an observational study done in a PICU of a tertiary care teaching hospital in Pune conducted over seven months starting from 1st June to 31st December, 2020 and which included the children meeting the case definition of PIMS-TS.

Results: A total 25 children were included of which 13 (52%) were males. Median age was 7 years. Fever of short duration was present in all children and 23 (92%) had gastrointestinal symptoms. 21 (84%) had features of shock while myocardial dysfunction was seen in eight (32%) children. Kawasaki disease like features were present in seven (28%) while five (20%) showed coronary artery dilatation. All had neutrophilia and lymphopenia while 10 (40%) showed thrombocytopenia. Interleukin-6 levels, done in six, and were found to be raised in all. SARS-CoV-2 RT-PCR and IgG antibody were positive in two while only IgG was positive in 14 (56%) children. Seven required mechanical ventilation while eleven were managed with HFNO. 16 (64%) children received both IVIG and steroids, two (8%) children received only IVIG while seven (28%) received only steroids. Two children each additionally received Tocilizumab and infliximab. 24 (96%) children survived.

Conclusions: Fever, gastrointestinal symptoms and hypotensive shock were predominant features of PIMS-TS. 2/3rd of children had demonstrable SARS-CoV-2 antibodies. Cardiac dysfunction was seen in 1/3rd of the children. It is a life-threatening illness requiring critical interventions, multi-organ support and various immunomodulators.

Keywords: IL-6, COVID-19, MIS-C, Kawasaki disease, Hyperinflammatory syndrome, Toxic shock syndrome

INTRODUCTION

COVID-19 in children has now been documented as a milder illness in children worldwide.¹ Initial data from India has also suggested a lower incidence of severe symptomatic presentations of COVID-19 in children.² There is however, a growing concern globally about consistent reports of a hyperinflammatory syndrome, mimicking Kawasaki disease (KD)/toxic shock syndrome, temporally associated to the COVID-19 pandemic, but

without compulsory demonstration of the viral infection through real-time reverse-transcriptase polymerase chain reaction (RT-PCR)/serology.³ The case definitions suggested by the several groups have significant overlap pertaining to the clinical profile as well as biochemical profile of the clusters of cases described.⁴⁻⁶ The current Indian data on pediatric inflammatory multisystem syndrome temporally associated with the SARS-CoV-2 (PIMS-TS) is scarce.

We hereby report a series of 25 cases of PIMS-TS and discuss the demography, clinical presentation, management and outcome of these children.

METHODS

This is an observational study in PICU of Bharati Vidyapeeth medical college and hospital, a tertiary care teaching hospital in Pune, India conducted over a 7-month period between 1st June to 31st December, 2020. Approval from the institutional ethics committee was taken and all children were included in the study after written informed consent of either of the parents. All children who met the criteria for the case definition of PIMS-TS as defined by Royal college of pediatrics and child health (RCPCH) were included.⁴ The data on demographic details, clinical presentation, laboratory and echocardiographic findings, treatment received, duration of hospital stay, and outcome was collected and analyzed. Chest radiograph was documented in all children with respiratory symptoms and signs including cough, difficulty in breathing and positive chest findings on examination.

Shock was defined as compensated or hypotensive based on presence of hypotension. Myocardial dysfunction was said to be present when echocardiogram showed decreased left ventricular ejection fraction (LVEF) <55% with or without elevated levels of troponin or brain natriuretic peptide (BNP). Children presenting with shock and left ventricular (LV) dysfunction on echocardiography were classified primarily as cardiogenic shock while those with distributive shock requiring vasopressor support were classified as vasoplegic shock. TaqMan[®] real-time PCR for SARS-CoV-2 and IgG antibody testing using in-house ELISA panel was done at an ICMR laboratory. Children were tested for influenza and other respiratory viruses by RT-PCR on nasopharyngeal samples and also for SARS-CoV-2 and enteric viruses (ROTA, Astrovirus, Adenovirus, Norovirus) on stool sample wherever possible. Multiplex PCR on nasopharyngeal samples was done in SARS-CoV-2 negative children using real time PCR kit by fast-track diagnostics (a Siemens Healthineers company). All children underwent evaluation of acute phase reactants, hemogram, coagulation profile, and liver and renal function tests. Interleukin-6 (IL-6) levels were done wherever feasible. Bedside functional echocardiography was performed by trained pediatric intensivists while echocardiography for cardiac and coronary artery abnormalities was done by trained pediatric cardiologist. The coronary artery diameters were measured as per standard criteria and indexed with z-scores.^{7,8} Coronary z-scores of greater than 2.5 were considered as dilated.⁷

Statistical analysis

Continuous variables are presented as median and interquartile ranges (IQRs), and categorical variables are reported as numbers and proportions. Statistical analyses were performed using SPSS version 24.0.

RESULTS

A total of 25 children were admitted in the PICU during the study period of six months. 52% (13) were males. Median age was 7 years (Interquartile range: IQR 3-12). All children resided in areas with high COVID-19 burden. One child had history of COVID-19 positive household contact while three had documented COVID-19 infection in the recent past.

All children (100%) had history of acute onset fever. 23 (92%) had gastrointestinal symptoms comprising of pain in abdomen, vomiting and / or diarrhoea. KD like features were present in seven (28%) children, characterised by non-purulent conjunctivitis, edema of hands and feet, macular rash over palms and soles. Comorbidities were present in 3 children of which 1 child had aplastic anemia and 2 had obesity with BMI greater than 95th percentile for age and sex. Presence of shock was seen in 21 (84%) children, and was predominantly vasoplegic in nature.

Neutrophilia and lymphopenia were seen in all ten (100%) children. Thrombocytopenia was seen in 10 (40%) children. C-reactive protein (CRP), procalcitonin, D-dimer, and ferritin were raised in all children as shown in table 2. The median CRP was 112 mg/dl (IQR 87-156), while median procalcitonin, D-dimer, and ferritin were 9.63 ng/ml (IQR 4.13-23.46), 1464 ng/ml (IQR 671-2949), 415 mg/dl (IQR 228-656) respectively. IL-6 levels done in six children were found to be raised in all with median of 303.5pg/ml (IQR 113.75-374.05). Median (IQR) for BNP (n=17) was 207 (99-637). Troponin-I was raised in three out of eight children with myocardial dysfunction while fibrinogen levels were increased in 23 (92%) children. Liver dysfunction was seen in eight (33%) in the form of deranged raised enzyme levels and prolonged prothrombin time. Serum albumin was low in 21 (84%). Two were RT-PCR and IgG antibody positive for SARS-CoV-2 while 14 (56%) others were positive for IgG antibodies. Multiplex PCR for tropical infections was found to be negative in all COVID-19 negative children. Blood culture was sterile in all children. Only two (8%) children had an abnormal chest radiograph, with one showing right lower lobe consolidation and the other showing bilateral pulmonary edema secondary to severe left ventricular dysfunction.

Six children (24%) had objective evidence of myocardial dysfunction with a reduced LVEF on echocardiography and raised BNP levels, three children had coronary artery dilatation and two children in addition had both left ventricular dysfunction as well as coronary artery dilatation. Seven children were mechanically ventilated, eleven required high flow nasal oxygen (HFNO) and three required oxygen by nasal prongs. Fluid resuscitation was required in 21 (84%) children with median fluid volume received being 30 ml/kg. Vasoactive drugs were required in 19 (76%) children with shock. Most frequently used vasoactive agent was dopamine followed by noradrenaline, vasopressin and dobutamine. While five children received stress dose intravenous hydrocortisone

for refractory shock, additionally one child received dexamethasone as therapy for hemophagocytic lymphohistiocytosis (HLH). As part of immune modulation 16 (64%) children received both IVIG (2 gm/kg over 12 hours) and methylprednisolone (10 mg/kg for 3 days), two (8%) children received only IVIG while seven (28%) received only methylprednisolone.

Tocilizumab was used in two children and infliximab in two children with KD like phenotype deemed refractory to steroid and IVIG. All children were given one broad spectrum antibiotic at the time of presentation. Aspirin was given in 23 (92%) children and low molecular weight heparin (LMWH) was given in 14 (56%) children. Median days of PICU and hospital stay were 4 and 7 days respectively. 24 children survived and are currently being followed up as part of continued surveillance.

Table 1: Demographic and clinical characteristics.

Characteristics	N=25
Female	12 (48%)
Age (years): median (IQR)	7 (3-12)
Duration of symptoms prior to hospitalization in days: median (IQR)	5 (range 3-10)
Symptoms	
Fever	25 (100%)
GI symptoms	23 (92%)
Skin rash	17 (68%)
Conjunctival congestion	16 (64%)
Breathing difficulty	7 (28%)
Shock	21 (84%)

Table 2: Baseline laboratory profile.

Laboratory tests (units) (n)	Median	Normal range
Hemogram (n=25)	Hemoglobin (gm/dl)	10.8 (8.1-13.6)
	Total WBC (/cmm)	8500 (6900-13800)
	Neutrophils (%)	80 (73-86)
	Lymphocytes (%)	11(7-16)
	Platelet count (/cmm ³)	181000(109500-276500)
Inflammatory markers	CRP, mg/ml (n=25)	112 (87-156)
	S. Ferritin (ng/ml) (n=25)	415 (228-656)
	Procalcitonin (ng/ml) (n=25)	13.59 (3.22-32.23)
	D-Dimer (ng/ml) (n=25)	1414 (671-2949)
	S. Fibrinogen (mg/dl) (n=20)	652(544-700)
	Serum IL-6 (pg/ml) (n=6)	303.5 (113.25-374)
Liver function tests (n=25)	Albumin (gm/dl)	3.1 (3-3.4)
	PT INR	1.36 (1.2-1.61)
	APTT (s)	36 (34-38.5)
Renal function test	Creatinine (mg/dl)	0.68 (0.55-0.76)
Cardiac markers	Pro BNP (pg/ml) (n=17)	207 (99-637)
	Troponin I (ng/ml) (n=9)	0.01 (0.01-0.04)
Reduced LVEF (EF <55%)	n=8	
Coronary dilatation (z score >2.5)	n=5	

Table 3: Treatment received and outcome.

Treatment and outcome	N=25
Fluid resuscitation	21 (84%)
Fluid volume required (median) (ml/kg)	30
Vasoactive drugs required	20 (80%)
IV methylprednisolone (10 mg/kg/dayx3 days)	23 (92%)
IVIG (2g/kg)	18 (72%)
Tocilizumab	2 (8%)
Infliximab	2 (8%)
Mechanical ventilation	7 (28%)
High flow nasal oxygen	11 (44%)
ICU stay in days: median (IQR)	4 (3-5)
Hospital stays in days: (median and IQR)	7 (5-10)
Death	1

DISCUSSION

The first report on epidemiological and clinical profile of COVID-19 in Indian children from our center studied in April-May, 2020 did not have any cases of PIMS-TS.² It was only after 8 weeks of this initial report that we encountered our first case of PIMS-TS starting June, 2020. All of these children were critically ill with two or more systems involved. The presentation of these cases with features of incomplete KD, toxic shock syndrome and HLH is consistent with studies reported in western literature.³ 21 (84%) children had features of hypotensive shock in the PICU of which 2 were fluid responsive while 19 required vasoactive drugs and respiratory support. The most notable finding was cardiac dysfunction and/or coronary dilatation, seen in 13 of the 25 children and among them three had both. Fever was the most common presenting symptom, seen in all followed by gastrointestinal symptoms (pain in abdomen and vomiting) in 92% of children, again coherent with reports worldwide. Seven (28%) out of 25 children had KD like features. The association between corona virus and hyperinflammatory syndromes like KD is known, and so are the temporal associations of increased numbers of inflammatory syndrome cases in relation to epidemics.^{9,10} However, though current reports of a multisystem inflammatory syndrome may partially or completely fulfill classic diagnostic criteria of KD, they differ from it in important ways including older mean age of presentation, shorter duration of fever, presence of multi-systemic involvement, elevation of D-dimer, procalcitonin and ferritin levels and relative thrombocytopenia in contrast to thrombocytosis.^{11,12} Epidemiologically, PIMS-TS has been seen in children who are RT-PCR negative with serology suggesting previous infection with COVID-19 as well as those with no preceding symptoms but exposure to positive contacts as was also seen in our study. These factors along with development of the syndrome after a 3- to 6-week lag may suggest that SARS-CoV-2 may be acting either as the trigger or an immune-modulating factor.¹³ Current experiences may help us understand why studies linking corona virus to KD in the past, and indeed multiple other organisms have not been able to consistently demonstrate viral infection in these children.¹⁴

The present cases fulfill the case definition of Pediatric inflammatory multisystem syndrome temporally associated with COVID-19 as proposed by RCPCH guideline.⁴ Three children had pre-existing comorbidities. 23 children in our study consistently reported gastrointestinal symptoms. The presence of a hypercoagulable state in COVID-19 is well documented and gastrointestinal (GI) involvement may be explained by gut/mesenteric ischemia due to microthrombi.¹⁵ GI symptoms may also imply route of viral entry or GI vasculitis due to inflammation. Pain in abdomen was a prominent complaint in all our children. In addition, one child showed significant gut edema as well as dilatation of large intestine on imaging. Seven children had features of incomplete KD. As reported previously, the clinical

spectrum of the syndrome rarely encompasses features of ARDS. The need for respiratory support is more often required as a part of shock management rather than due to primary respiratory failure.¹⁶ Findings in our children were consistent with the same as only one of the children had pulmonary involvement in the form of right lower lobe consolidation on chest radiograph which resolved subsequently. Considering the rare occurrence of respiratory system manifestations, a high index of suspicion is warranted to diagnose these children early in the course of the disease.

All our children showed a significant elevation in inflammatory markers (CRP, procalcitonin, D-dimer, ferritin), all of which showed a gradual reduction concurrent with clinical response. The elevation in these markers has been routinely reported in PIMS-TS cases across the globe.¹⁷ IL-6 done in six children was also found to be raised highlighting the cytokine mediated phenomenon. One child had several unusual features including HLH and features of hemorrhagic encephalitis, both of which have not reported till date in PIMS-TS. The background of aplastic anemia contributed significantly to diagnostic challenges. Infection induced HLH can occur with aplastic anemia but is not commonly reported.¹⁸ Her renal function which was deranged on admission normalized within 24 hours after optimization of circulation. Liver involvement could be interpreted as part of HLH spectrum, or as related to the infectious trigger. Her MRI brain revealed features suggesting hemorrhagic encephalitis including multiple bilateral hemorrhages in cortex, white matter and cerebellum with areas of restricted diffusion and gradient blooming. Hemorrhagic encephalitis is either a form of ADEM/post infectious phenomenon.^{19,20} The understanding remains that this represents the most severe end of the spectrum of hyperinflammation. Though acute phase reactants are elevated in both sepsis and PIMS-TS, hypofibrinogenemia is prominent in DIC, HLH, and also in acute liver failure. The presence of elevated fibrinogen in spite of these conditions being present probably implied hyperinflammation. Hemorrhagic encephalitis has been reported on two instances in COVID-19 PCR positive adults.^{21,22} As noted in one of those reports, an underlying aplastic anemia may have contributed to the hemorrhagic component of the encephalopathy.

Shock was predominantly vasoplegic in all children; though eight children also showed objective evidence of myocardial dysfunction based on echocardiography and cardiac enzymes. Fluid resuscitation was required in all with a median of 30ml/kg fluid boluses including crystalloids and colloids. All children had hypotension most commonly requiring dopamine followed by noradrenaline, dobutamine and vasopressin. Intravenous hydrocortisone was given in five children as part of management of refractory shock. Despite hypotension being universal in those with shock, eight of the 25 children showed objective evidence of left ventricular dysfunction of which two also had coronary artery

dilatation. Three children had isolated coronary artery dilatation. This experience is in coherence with the series from UK and Europe where majority of children with PIMS-TS had systemic hypotension and left ventricular dysfunction while a small proportion had coronary artery involvement in the form of objective dilatation or appearing echo-bright on echocardiography.^{23,24} Two children had a significant component of myocardial dysfunction and clinically presented as a cold, hypotensive shock with normal pulse pressure. Sepsis being the most common differential for these children, must be actively ruled out. Elevated levels of acute phase reactants like CRP, ferritin, D-dimer and fibrinogen are common to both sepsis and PIMS-TS. All our children received one broad-spectrum antibiotic at the time of presentation. However, concurrent bacterial infection was ruled out by blood culture in all children and multiplex PCR in those who were RT-PCR negative.

Though the clinical presentation of this entity with multi-organ involvement shows considerable overlap with KD, the optimal immunomodulatory therapy for PIMS-TS has not been established universally. In our series, one patient responded clinically to hydrocortisone with improvement in inflammatory parameters as well and hence did not receive methylprednisolone or IVIG. Based on current recommendations/evidence, early recognition followed by use of steroids and IVIG in the absence of any microbial infection form crux of immune-modulation.^{25,26} One child received multiple therapies due to her predisposition to develop HLH as well as the clinical and biochemical overlap with PIMS-TS. 16 (64%) children received the dual immunomodulation therapy of methylprednisolone and IVIG to which they showed a sustained response while two children responded only to IVIG not requiring steroids. 14 (56%) children in our series were given LMWH and aspirin in anti-inflammatory dose followed later by anti-platelet doses irrespective of presence of KD like features, while nine (36%) were given only aspirin. However, the role of these agents in treating the hyper-inflammation in PIMS-TS remains equivocal.

The strength of our study is that we have captured the clinical and laboratory details in depth including IL-6 levels with extensive evaluation for etiological diagnosis. That being said, the limitations of our study lie in the fact that ours is a single center experience and with total number of cases being lesser, the findings may not be representative of the entire spectrum of the entity of PIMS-TS which will require ongoing surveillance. Also, considering the unfamiliarity of the disease pathogenesis and evolving management strategies, there is no definite guidance in terms of therapy yet. This adds to the therapeutic limitations wherein we have manipulated therapeutic interventions as per current recommendations and our understanding of the clinical and biochemical profiles of the cases. The long-term outcome of these children in terms of cardiovascular function and persistent coronary abnormalities remains to be seen with evolution

of solitary treatment recommendations likely to be established in the future.

CONCLUSION

In conclusion, PIMS-TS is a life-threatening syndrome seen mostly in children above 5 years of age. Fever, gastrointestinal symptoms and hypotensive shock are predominant features requiring critical interventions. Though there may be overlap of mucocutaneous features; older age, shorter fever duration, abdominal pain and absence of thrombocytosis differentiate PIMS-TS from KD. One third of children had left ventricular dysfunction and/or coronary artery abnormalities. Early recognition, multi-organ support and immune-modulation using steroids and IVIG results in quicker recovery with favorable outcomes. Biological drugs may be used in refractory cases in consultation with pediatric rheumatologist. It is therefore imperative for pediatricians to be aware of this entity, and report their experiences to accelerate understanding of the disease spectrum, its evaluation and treatment.

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