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Original Research Article

Clinical, biochemical and echocardiographic characteristics in children with multisystem inflammatory syndrome associated with coronavirus disease: a tertiary care experience

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ABSTRACT

Background: We describe the clinical, biochemical and echocardiographic characteristics in children diagnosed with multisystem inflammatory syndrome (MISC) temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2), admitted to a tertiary care hospital in Goa, India.
Methods: This was a retrospective observational study conducted at Goa Medical College, Goa, India. Parameters including demographics, clinical features, laboratory markers, medications and outcomes were obtained from patient hospital records; analyzed for patients treated for MISC (as per WHO case definition) for a period of 11 months from 01 July 2020 to 31 July 2021.
Results: 30 patients (18 males) with median age of 7 years (IQR: 2 months – 12 years) were included. The proportion of children with gastrointestinal symptoms was 20 (64.5%), shock was a presenting feature in 15 (48%) and coronary ectasia and/or low ejection fraction was seen in 12 children (38.7%).
Conclusions: A high index of suspicion for the diagnosis of MIS-C in children presenting with fever and Kawasaki disease like symptoms or signs of shock is recommended; since early aggressive therapy with Intravenous Immunoglobulins and methylprednisolone can have favourable outcomes.

Keywords: COVID-19, MIS-C, Kawasaki disease, IVIG, Methylprednisolone

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) pandemic began in December 2019 affecting a large population worldwide. Though a large number of children who suffered from this infection were asymptomatic, a novel inflammatory syndrome with multisystem involvement (MIS-C) was seen affecting the children on a large scale. Multisystem inflammatory syndrome in children (MIS-C) associated with COVID- 19 also called as pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (PIMS-TS) is a hyperinflammatory syndrome occurring in close temporal association with a SARS-CoV-2 infection in children.[1,2] Since its initial reports from Europe, several cases have been reported worldwide. We conducted this study to assess the various clinical, biochemical and echocardiographic characteristics in children affected by this syndrome who presented at our institution in Goa, India.

METHODS

This was a retrospective observational study conducted in Goa Medical College, a tertiary care teaching hospital in Goa, India; using data from hospital patient records obtained from the medical records department of the

hospital, from July 2020-July 2021. Sample size was calculated based on census method. Ethics committee clearance was obtained from the college ethics committee. Data was entered on a Microsoft excel spreadsheet. Statistical analysis was done using median and percentages.

All children fulfilling the World Health Organization (WHO) case definition for MIS-C admitted in our institute during the study period were included. Infective causes like dengue, malaria, leptospirosis, scrub typhus and bacterial sepsis was excluded by appropriate investigations. Mucocutaneous features such as skin rash, non-purulent conjunctivitis, changes in lips, oral mucosa and extremity changes as defined by previous guidelines of Kawasaki disease and MIS-C were noted.[1,3]

Shock was defined as hypotension with poor peripheral perfusion requiring inotropic support and/or fluid resuscitation >20 ml/kg. Total and differential white blood cell count, platelet count, acute phase reactants (C-reactive protein, ferritin, procalcitonin, lactate dehydrogenase (LDH), D-dimer, interleukin-6), renal and liver function tests were also recorded. Laboratory parameters were labeled as normal or deranged in relation to the age-specific normal ranges.

Echocardiography, done by trained ECHO technician was used to assess myocardial dysfunction and ectasia or aneurysm of the coronary arteries. Low ejection fraction was defined as LVEF <50% on echocardiography and coronary Z scores of greater than 2.5 were considered as coronary ectasia/aneurysm.[3]

SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) was done in all patients, and SARS-CoV-2 antibody testing was done by detecting receptor binding domain of SPIKE protein S1 using ELFA technology (mini VIDAS/VIDAS).

RESULTS

Of the 30 patients who were diagnosed to have MISC; 18 were males and 12 females. The age group varied from 2 months old infant to 12-year-old child. Of the 30 children, 4 tested positive for COVID-19 by RTPCR at the time of diagnosis of MISC hence their antibody titres were not done; while Covid antibody titres were strongly positive in all the remaining 26 children and they were negative for COVID-19 by RTPCR.

The duration of illness prior to hospital admission ranged from 1 to 15 days.

Duration of hospital stay ranged from 3 to 36 days in those who survived, and 1 to 26 days among the 6 children who expired. (Table 1).

Biochemical evaluation showed serum ferritin levels ranging from 24.6 to 40000 ng/ml with 20 patients having values more than 500 ng/ml (66.67%); procalcitonin levels ranged from 0.06 to 136.27 ng/ml with 24 patients having values >1 ng/ml (80%), LDH ranged from 183 to 3325 U/l with 28 patients having values above 200 U/l (93.3%).

Table 1: Demographic and clinical parameters in children with MIS-C.

Characteristic	Total cases n=30 (%)	Deaths n=6 (%)
Age	2 months-12 years	2 months-9 years
Male: female	18M: 12F	2M: 4F
RTPCR positive	4 (13)	1 (16.6)
Antibody positive	26 (86.6)	5 (83.3)
Symptoms		
Fever	29 (96.6)	6 (100)
Rash	15 (50)	2 (33.3)
Abdominal pain	20 (66.6)	2 (33.3)
Diarrhoea/vomitting	20 (66.6)	2 (33.3)
Conjunctivitis	16 (53.3)	3 (50)
Mucositis	4 (13.3)	1 (16.6)
Shock	15 (50)	4 (66.6)

D-dimers were done in 18 children and the values ranged from 8.9 to 5887 ng/ml with 11 patients having values more than 1000 ng/ml (61%). IL 6 levels were done in 7 children and ranged from 314 to 2287.1 pg/ml and all patients had values more than 35 pg/ml (100%).

Table 2: Biochemical and echocardiographic parameters and management in children with MIS-C.

Characteristic	Total n=30	Deaths n=6
Neutrophil: lymphocyte ratio >2	28	6
Platelet count <1 lakh	9	3
Serum ferritin >500 ng/ml	20	4
Procalcitonin >1 ng/ml	24	6
LDH >200 IU/l	28	6
D-dimer >1000 ng/ml	11 of 18	2 of 3
IL-6 >35 pg/ml	7 of 7	2 of 2
Deranged coagulation profile	6 of 25	5
Elevated serum creatinine	8	3
Deranged liver enzymes	8	3
ECHO findings		
Coronary ectasia and/or low ejection fraction	12	5
Treatment		
Methylprednisolone	7	2
IVIG + methylprednisolone	22	4
No treatment	1	0
Aspirin	10	0
Inotropes (single/more than 1)	14	5
Enoxaparin	2	1

The neutrophil: lymphocyte ratio varied from 0.9 to 47.5 with 28 patients having ratios more than 2 (93.3%). Platelet count ranged from 0.313 to 4.4 lakhs and 9 patients had values below 1 lakh (30%).

The coagulation profile i.e. prothrombin time and INR was done in 25 patients and was found to be prolonged in 6 patients (24%). Serum creatinine values and liver enzymes were raised in 8 patients (26%). Shock was a presenting complaint in 15 patients (50%), wherein 1 child received fluid resuscitation alone, while 6 patients required a single inotrope and 8 patients required two inotropes. Coronary artery ectasia and/or reduced ejection fraction on echocardiography was seen in 12 patients. 22 patients were treated with intravenous immunoglobulin along with IV methylprednisolone while 7 patients received only IV methylprednisolone and 1 child with mild symptoms recovered spontaneously (Table 2).

DISCUSSION

A novel hyperinflammatory condition with severe multisystem involvement has been described in children and adolescents during the COVID-19 pandemic. We started seeing patients with MIS-C soon after the first wave of COVID-19 cases in Goa in July 2020, and our first case was diagnosed in September 2020; followed by another wave of COVID from April to July 2021 with corresponding increase in MISC cases during the same period. (Figure 1).

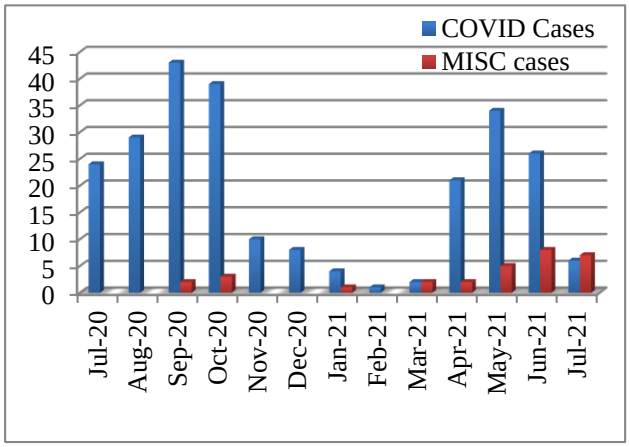

Figure 1: Temporal association of MISC cases with COVID cases in children during the two waves of COVID in Goa.

As noted in Figure 1, of the 30 cases that were recorded during the study period, only 6 cases were recorded in the first 8 months while remaining 24 cases were recorded in the later 5 months probably due to better understanding of the syndrome and high index of suspicion.

Consistent with published data from across the globe and many Indian studies, children in our study also presented with fever, rash, gastrointestinal symptoms and shock.[4-9]

The median age of children in our study was 7 years (2 months to 12 years) with 76.6% of affected children above the age of 5 years, which was similar to various studies done in Indian children.[4,6-11]

Our study had a male preponderance (60%) similar to previous reports although Dhanlakshmi et al, Jain et al and Shobhavat et al recorded a female preponderance probably due to fewer number of patients studied.[4-9,11]

A low incidence of RT-PCR positivity (13%) with a high presence of SARS-CoV-2 antibodies (86.6%) was seen in our study similar to studies done in Southern and Western India while Gupta et al and Maheshwari et al reported higher RTPCR positivity rate in children with MIS-C in North India.[4-6,8-11]

Mortality rate among patients in our study was 20% while Maheshwari et al reported mortality of 34.5%.[10] A very high mortality of 60% was reported by Gupta et al attributed to delay in diagnosis and referral; while most other studies reported low mortality rates (0 to 14%).[4-9,11]

As noted in Figure 2, four out of 6 deaths were recorded in the first 8 months of study period while the last 2 months did not record any deaths probably due to prompt diagnosis and early aggressive treatment (Figure 2).

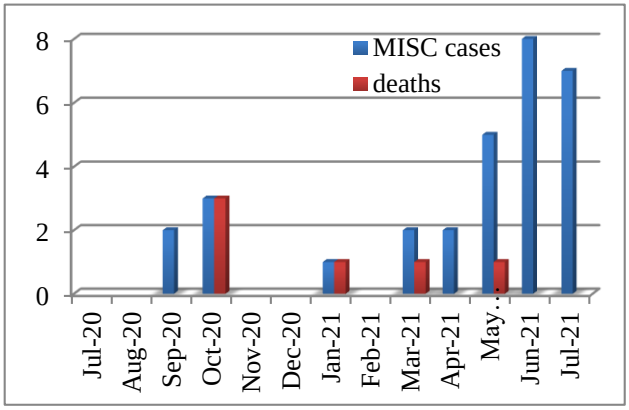

Figure 2: Number of deaths from MISC in relation to total cases recorded.

Of the 6 children who did not survive in our study, there was female preponderance (66.7%), age above 5 years (66.7%) and only one child was RT-PCR positive for SARS-CoV-2, while the remaining 5 had high titres of SARS-CoV-2 antibodies (83.3%). We noted derangement in coagulation profile of 5 patients (83.3%) and elevated serum creatinine and liver enzymes in 4 patients (66.7%). Shock with echocardiographic evidence of cardiac dysfunction was seen in 5 patients (83.3%) who succumbed despite receiving fluid resuscitation, multiple inotropes and mechanical ventilation. 4 patients received IVIG and IV methylprednisolone while 2 received only IV methylprednisolone since they expired within 48 hours of hospital stay. Thus, coagulopathy and shock were distinct features among the non survivors in our study. As

emphasized in the systematic review by Sachdeva et al, the treatment is partly dependent on the presenting condition of the patient and has been evolving with the availability of a wide range of therapeutic options.[12]

22 of our patients received IVIG plus methylprednisolone, 18 of who survived (82%) supported by the study by Wang et al who reported a better clinical efficacy with IVIG plus methylprednisolone as compared to IVIG alone, although none of our patients received IVIG alone.[13] Also, 7 children received methylprednisolone alone of which 5 survived (71%).

Limitations

A limitation of our study was that only the immediate outcomes were analysed. Secondly, all laboratory parameters such as d dimer, IL 6, troponin I and coagulation profile were not done in all patients.

CONCLUSION

Shock, coagulopathy, renal dysfunction and hepatic enzyme derangement along with cardiac dysfunction at the time of admission seemed to be poor prognostic factors in our study. A good outcome with IVIG plus methylprednisolone was also established. Hence, a high index of suspicion for the diagnosis of MIS-C in children presenting with fever and Kawasaki disease like symptoms or signs of shock is recommended; since early aggressive therapy with intravenous immunoglobulins and methylprednisolone can have favourable outcomes.

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