Original Article

Clinical Profile and Immediate Outcome of Multisystem Inflammatory Syndrome in Children Associated with COVID-19: A Multicentric Study

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Abstract

Introduction: Following an asymptomatic or mildly symptomatic coronavirus disease (COVID-19), otherwise healthy children may develop serious manifestations in the form of cardiac, neurological, respiratory, gastrointestinal, and dermatologic dysfunction. Many such cases were being observed in Odisha, an eastern state of India, and have been reported from different health-care facilities. We related these unexplained serious manifestations to multisystem inflammatory syndrome associated with COVID-19 (MIS-C) and planned this study. **Methods:** This retrospective observational study was carried out at the following three tertiary care centers: Kalinga Institute of Medical Sciences, Bhubaneswar; MKCG Medical College, Berhampur; and Jagannath Hospital, Bhubaneswar. The study population included all children aged from 1 month to 18 years admitted to the hospitals with MIS-C according to the WHO diagnostic criteria. All the data were analyzed by SPSS software. **Results:** A total of 21 children were included in our study. Majority of the cases were male (76.2%), and the predominant age group was 6–10 years (47.6%). Common symptoms and signs in our observation included fever, pain abdomen, seizure, and hypotension. Most of these cases were positive for severe acute respiratory syndrome coronavirus antibody (80.95%). Response to immunotherapy was dramatic. Mortality (9%) of our study was higher than 1.8%–3% from that of Western literature. None of our patients had coronary abnormality, while two patients had mild cardiac dysfunction at discharge comparable to that of other studies. **Conclusion:** MIS-C following exposure to COVID-19 infection in children is a clinical syndrome, which needs early suspicion and appropriate intervention to prevent mortality.

Keywords: COVID-19, COVID antibody, immunotherapy, inflammation, multisystem

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is a novel coronavirus which continues to spread and remains a threat to human life across the globe. The pediatric population infected with the virus are usually asymptomatic or exhibit mild symptoms. Multisystem inflammatory syndrome in children (MIS-C) is a new dangerous childhood disease that occurs weeks after a mild or asymptomatic SARS-CoV-2 infection. This occurs 3–4 weeks after an asymptomatic infection. Otherwise healthy children may manifest some combinations of cardiac dysfunction, gastrointestinal problem, fever, fatigue, or rash. This is postulated to be related to systemic inflammatory response due to coronavirus disease (COVID-19). This rare syndrome shares common features with other pediatric inflammatory conditions including Kawasaki disease (KD), staphylococcal and streptococcal toxic shock syndromes (TSSs), bacterial sepsis, and macrophage activation syndrome. Many such cases are being observed in our state and reported from different health-care facilities; hence, we related these unexplained serious manifestations in some of the children to MIS-C. Hence, we planned to conduct a retrospective study on these observations. In this multicentic record-based study, we

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analyzed the data to have a clearer image of disease spectrum for early recognition and management.

Methods

The first case of MIS-C in Odisha was detected in the 1st week of August 2020, corresponding to the surge of COVID-19 cases in late May and June 2020 onward. This study was conducted after taking permission from the institutional ethics committee (KIIT/KIMS/IEC/541/2021). Data were collected from the medical records of three tertiary care centers of Odisha, an eastern Indian state. All the cases adhering to the WHO definition of MIS-C were included in the study.[1]

The criteria for case definition of MIS-C are as follows: fever for a minimum of 3 days, and any two of the following, (i) skin rashes or bilateral conjunctival congestion or muco-cutaneous inflammation signs; (ii) hypotension or shock; (iii) myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiography findings or elevated Troponin/NT-proBNP); (iv) coagulopathy (v); and gastrointestinal problems (diarrhea, vomiting, or abdominal pain). Markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or procalcitonin have to be high in the absence of infective causes of inflammation, including bacterial sepsis and staphylococcal or streptococcal shock syndromes. There has to be evidence of COVID-19 (reverse transcription polymerase chain reaction [RT-PCR], antigen test, or serology positivity), or likely contact with patients with COVID-19.

The data collected were entered in Microsoft Excel spreadsheet and imported to IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Continuous variables were expressed as means and standard deviations, and categorical variables were expressed as percentages.

Results

A total of 21 cases of MIS-C from the 1st week of August 2020 to the 2nd week of September 2020 were seen [Tables 1 and 2]. Out of them, 15 (71.4%) were boys, whereas 6 (28.6%) were girls. We found three (14.3%) cases between 1 and 5 years of age, while ten (47.6%) cases were aged between 6 and 10 years, six (28.6%) cases between 11 and 15 years, and two (9.5%) cases were aged above 15 years. The mean age of the patients was 9.09 years. Fever was found in all (100%) cases, while abdominal symptoms were found in 14 (66.7%) cases [Table 2]. Loose motion, vomiting, and abdominal pain were the presenting complaints in 4 (19%), 10 (47.6%), and 11 (52.4%) cases, respectively. Respiratory distress at admission was found in nine cases (42.8%), while hypotension at admission was found in ten (47.6%) cases. Ten (47.6%) children had some form of neurological involvement such as seizures, agitation, or altered sensorium. Seizure was one of the manifestations in five (23.8%) cases. Skin rash was found in nine (42.9%) cases, while conjunctival congestion was found in eight (38.1%) cases. The mean total leukocyte count (TLC) was 13,800/mm^3, neutrophil was 72%, lymphocyte count was 22%, and the mean platelet count was 2.40 lakh/mm^3. The inflammatory markers such as C-reactive protein (CRP) mean value was 52.2 mg/dL, procalcitonin level was 14.9 ng/mL, while the mean ESR was 76.4 mm in the 1st h. The mean value of ferritin was 530 ng/mL and that of LDH was 802 U/L, while the mean D-dimer value was 3.832 µg/ml. Laboratory evidence of SARS-CoV-2 was found in 19 patients; 2 were RT-PCR positive, 17 were IgG antibody positive, while 2 had both RT-PCR and antibody positivity. In two children, RTPCR and antibody were negative, but their parents were RT-PCR positive 4 weeks before. Out of 21 patients, 9 (42.9%) received IVIG, while 19 (90.4%) received steroids, and only steroid was used in 11 children [Table 3]. Out of the two children who left against medical advice, one child did not receive any

Table 1: Demographic characteristics

Characteristics	*n*(%)
Age group (years)	
<1	Nil
1-5	3
6-10	10
11-15	6
>15	2
Sex (male: female)	15:6
Mean age (years)	9.09
Comorbidities	Nephrotic syndrome (1=4.8%)
RTPCR positivity	4
Rapid antigen positivity	0
Antibody positivity	17
RTPCR+antibody positivity	2
Both negative	2
Outcome, *n* (%)	
Discharged	17 (81)
LAMA	2 (9.5)
Death	2 (9.5)
Mean duration of stay (days)	11

RT-PCR: Reverse transcription-polymerase chain reaction, LAMA: Left against medical advice

Table 2: Clinical characteristics

Clinical Presentation	*n* (%)
Fever	21 (100)
Abdominal symptoms	14 (66.7)
Loose motion	4 (19)
Vomiting	10 (47.6)
Pain abdomen	11 (52.4)
Hypotension	10 (47.6)
Seizures	5 (23.8)
Respiratory distress	9 (42.9)
Congestive heart failure	1 (4.8)
CNS involvement	10 (47.6)
Conjunctival congestion	8 (38.1)
Skin rash	8 (38.1)

CNS: Central nervous system

Table 3: Therapeutic options utilized

Therapeutic option	*n* (%)
IVIG	9 (42.9)
Steroid	19 (90.4)
Only steroid	11 (52.4)
Only IVIG	1 (4.8)
IVIG + steroid	8 (38.1)
NIV	2 (9.5)
Invasive ventilation	2 (9.5)
LMWH	10 (47.6)
Inotrope	10 (47.6)

IVIG: Intravenous immunoglobulin, LMWH: Low-molecular-weight heparin, NIV: Noninvasive ventilation

treatment. Invasive ventilation was required for two (0.95%) patients, while noninvasive ventilation (NIV) was used for two (0.95%) children. Inotropic support was required in ten (47.6%) patients. Echocardiography was done in 17 cases: myocardial dysfunction was found in 8 (38.1%), 3 had mild pericardial effusion, while none had coronary dilatation. Creatinine phosphokinase (CPK MB) was done in only six patients, and it was elevated in five patients. CPK MB test was not available at one center.

Out of the 21 patients, 17 recovered, while 2 left against medical advice and 2 died. Out of the two children who died, one had comorbidity such as nephrotic syndrome and the other one died of respiratory complications. None of our patients had coronary abnormality, while two patients had mild cardiac dysfunction at discharge.

Discussion

Among the 21 cases, the mean age in our study population was 9.09 years, which is comparable to the mean age of 9.5 years in a study done by Sadiq *et al*. in Pakistan.[2] Three cases were below 5 years of age and 2 cases were above 15 years, while majority (76.2%) were in between 5 and 15 years' age group, which points toward the vulnerable age group. Though there is a clinical resemblance toward atypical KD, unlike KD, these cases have occurred in older children and adolescents. Many studies from the USA and Europe have similar age distributions as observed in our study group.[3-6] Selva *et al*. found marked differences between the antibody responses in children and adults against coronavirus. These varying responses were associated with different Fcγ receptor-binding properties.[7] Differences in antibody response might contribute to such specific age distribution in our study population.

All children in our study with features of this new inflammatory syndrome fulfilled the WHO criteria for MIS-C for the clinical, laboratory, and echocardiographical features [Table 4].[1] Skin rash was found in nine (42.8%) cases, while conjunctival congestion was found in eight cases (38.1%). Nearly 48% of our children presented with shock and required volume resuscitation and inotropic support. KD-like features of the syndrome seem to be predominant in some case series (Italy).[8] However, case reports from France and the UK have more acute presentation with shock with features of TSS.[3,6] However, these data are reported mostly from intensive care unit admissions rather than the general pediatric population. The US data also showed atypical KD-like features in 40% of the patients.[5] However, this variability in clinical manifestations is difficult to distinguish on clinical ground. Out of 11 patients who had some form of central nervous system involvement, 5 of them had clinical seizures, which adds further to the wide clinical distribution of MIS-C. Magnetic resonance imaging (MRI) of brain was done in three out of five children with seizures. One child had features of cerebral edema, while two others had normal MRI findings. The child with cerebral edema had normal blood pressure, while the other two children had features of shock. Hence, transient cerebral hypoperfusion as the cause of seizures cannot be ruled out in them. Chen in his review of six reports on MIS-C found that out of 187 children, 38% had neurological issues.[9] The exact cause of this neurologic complication is not known, but it seems to be different from adult COVID-19 cases where the usual cause is cerebrovascular thromboembolism. Postinfectious immune response might be responsible for neurologic manifestation.[9] In a study published in *JAMA Neurology*, out of 616 MIS-C cases, 126 (20.4%) children had neurologic involvement. Of the 126 children, 20 had life-threatening neurologic conditions such as severe encephalopathy, stroke, acute demyelinating encephalomyelitis, acute fulminant cerebral edema, or Guillain–Barre syndrome.[10] Only nine (42.8%) cases had respiratory distress at admission. One child had features of acute respiratory distress syndrome (ARDS) and the rest eight children had features of either shock or pulmonary edema. Godfred-Cato *et al*. in an USA cohort had reported significant respiratory involvement (63%) in MIS-C. Those patients had higher incidence of RT-PCR positivity and higher mortality rate.[11] In our series, the child who developed ARDS was found to be RT-PCR positive, and she expired despite all supportive care.

Out of the 21 cases, 10 (48%) children presented with shock and required volume resuscitation and inotropic support. Echocardiography was done in 17 cases: myocardial dysfunction was found in 8 (38.1%), while we were not able to detect coronary dilatation in any patient. All the cases responded to the supportive treatment. Ramcharan *et al*. in their cohort of 15 cases of MIS-C, who were referred for cardiac evaluation, found cardiac dysfunction in 63% of the cases, whereas coronary abnormalities were detected in 93% of the cases.[12] In a recent study from Mumbai, coronary affection was found in 23.8% of cases.[13]

In the present study, the mean TLC was 13,800/mm^3 with a mean neutrophil of 72% and lymphocyte of 22%, which is comparable to the meta-analysis done by Lagunas-Range *et al*. who could find an association between the high white cell count, low lymphocyte count, low platelet count, elevated CRP, and severity.[14] In three patients, thrombocytopenia (<1.5 Lakh/mm^3) was found, but none

Table 4: Proportion of patients fulfilling individual WHO criteria

Serial number	WHO criteria	Number of patients, *n* (%)
1	Children aged 0-19 years	21/21 (100)
2	Fever more than 3 days	21/21 (100)
3 (i)	Rashes, conjunctival congestion	4/21 (19)
3 (ii)	Hypotension, shock	10/21 (47.6)
3 (iii)	Myocardial dysfunction, valvulitis, pericarditis, coronary abnormality (ECHO and troponin, NT ProBNP)	8/17 (47)
3 (iv)	Coagulopathy (PT, PTT, D-dimer)	18/18 (100)
3 (v)	GI symptoms	14/21 (66.7)
4	Inflammatory markers CRP, ESR, procalcitonin	CRP 18/20 (90)
5	No obvious cause	21/21 (100)
6 (i)	RTPCR/rapid antigen positivity	4/21 (19)
6 (ii)	Antibody positivity	17/21 (80.9)
6 (iii)	Close contact with COVID case in past	2/21 (9.5)

ECHO: Echocardiography, NT: N-terminal, proBNP: Protein B-type natriuretic peptide, PT: Prothrombin time, PTT: Partial thromboplastin time, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RTPCR: Reverse transcription-polymerase chain reaction, COVID: Coronavirus disease

had very low platelet count, which could be a point to distinguish this syndrome from severe sepsis or dengue. The inflammatory markers such as CRP, ESR, and procalcitonin were elevated in our enrolled patients with a mean CRP of 52.2 mg/dL. There is increasing evidence in adult studies, that raised levels of CRP are associated with severity and mortality in COVID patients.[15] Majority of our patients have shown positive IgG to SARS-CoV-2, which points toward an association with past COVID infections in these patients. In two cases where both RTPCR and antibodies were negative, the epidemiological connection with past COVID-19 infection could not be ignored, as their parents were RTPCT positive 4 weeks back. The mean D-dimer value was very high (3.832 μg/mL), which is comparable to the elevated D-dimer levels in both pediatric and adult patients with COVID-19.[16] Evidence from adult studies suggests that elevated D-dimer levels are associated with poor outcome, but therapeutic implications of the high D-dimer are not yet clear.[17] A recent pediatric guideline suggests thromboprophylaxis in children with COVID-19 with risk factors for thrombosis such as presence of central venous catheter, decreased mobility, and past or family history of thromboembolism.[18,19] The American College of Rheumatology has recommended the use of therapeutic anticoagulation for cases with ejection fraction <35%, documented thrombosis, and coronary artery *z* score of >10.[20] It is still not clear whether MIS-C patients have similar risk of thrombosis like that of acute COVID patients. However, as these patients have high D-dimer along with multiorgan dysfunction requiring critical care treatment, it is reasonable to start low-molecular-weight heparin (LMWH) for MIS-C.[20] We used LMWH in our patients as per the above guidelines. Myocardial dysfunction was found in 38.1% of patients, while none had coronary dilatation in their first echocardigraphy in our study.

Among the 21 patients, 9 received IVIG (1–2 g/kg), but a higher percentage of patients received steroids. In eight children who received IVIG, intravenous methyl prednisolone was given at a dose of 1 mg/kg/day for few days followed by oral prednisolone 1 mg/kg/day for 2 weeks (tapered). The decision of IVIG or steroid or both was taken based on clinical presentation, severity at presentation, and status of cardiac involvement. Out of 11 children who received only steroid, two children were treated with pulse methyl prednisolone 10 mg/kg/day for 3 days, followed by oral prednisolone at a dose of 1 mg/kg/day for 2 weeks and both of them improved. In other nine patients without significant cardiac involvement, methyl prednisolone was used at a dose of 1 mg/kg/day for few days followed by tapered dose of prednisolone for 2 weeks. [Table 3] Due to overlap of clinical features, many clinical trials have proposed IVIG as the first choice in the treatment of MIS-C.[20,21] Whittaker *et al*. reported 100% use for KD-like presentations, 72% for those with shock, and 61% for those with fever and inflammation alone.[4] With such variation in the management of MIS-C patients, there is suboptimal evidence to assess the superiority of various treatments. In our study, 47.6% of the patients required inotropic support despite adequate fluid resuscitation. Early recognition of shock, judicious fluid resuscitation, timely initiation of inotropes, and vasopressors are key factors for favorable outcome. NIV was required in two children for respiratory distress with shock. Similarly, invasive ventilation was required in two children: one for a child with RTPCR positivity with respiratory involvement and the other one, a case of nephrotic syndrome with multiorgan dysfunction. Both the children requiring invasive ventilation expired. In one of the largest cohorts from the USA of 570 cases of MIS-C, 38.1% needed some form of respiratory support, while in another case series from Mumbai, 39.1% required invasive respiratory support.[10,22] Mortality (9%) of our study was higher to 1.8%–3% from that of the Western literature. None of our patients had coronary abnormality, while two had mild cardiac dysfunction at discharge, comparable to that of other studies.

Conclusion

Multisystem inflammatory syndrome is a serious and life-threatening disease in children, which mandates multispecialty involvement as cardiac and neurologic complications are significantly high. Diagnosis and management of MIS-C is a challenge as the guidelines are evolving and new data are coming up in literature. Pediatricians should familiarize themselves with the presentation of this new disease and start aggressive multispecialty management. Immunotherapy is the cornerstone in management; however, selection of the exact drug may need further studies.

Research quality and Ethics statement

This study was approved by the Institutional Review Board/ Ethics Committee approval number KIIT/KIMS/IEC/541/2021. The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during the conduct of this research project.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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