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Treatment of MIS-C in Children with Only Steroid - Our Experience in a Tertiary Health Care Center in Rural Bihar

Swapan Kumar Ray, Debjit Saha, Manbir Singh, Abhay Kumar, Praveen Kumar, Sreemayee Kundu, Shreemant Gautam, Shivesh Jha, Gurdeep Singh, Aakanksha Tripti

Abstract

Introduction: During the COVID pandemic, initially the children were less affected or were asymptomatic. Later in 2021 many children and adolescents who suffered from COVID-19 infection either symptomatic or asymptomatic, got serious complication known as Paediatric Multisystem Inflammatory Syndrome (MIS) associated with severe acute respiratory syndrome coronavirus 2 (also known as MIS in children [MIS-C]). We admitted many such cases of MISC from surrounding community of Kishanganj located in Bihar. Clinical presentations were fever, shock with hyper-inflammation, and multiorgan dysfunction, neurological, cardiological, and gastrointestinal dysfunction. This complication of COVID 19 infection was likely a post infection hyper-inflammatory response as almost 90% of these children were tested positive for antibodies against CoV-2 with significant rise in inflammatory markers and cytokine levels. Intravenous immunoglobulin (IVIG), aspirin, low molecular weight heparin, and steroids were the cornerstones of treatment protocol. We report here 41 cases of similar presentation, treatment, and outcome of children from Pediatrics Department of MGM Medical College, Kishanganj, Bihar. **Materials and Methods**: Forty-one cases suspected of MIS-C fulfilling the criteria set by the WHO were taken for this study at Mata Gujri Memorial Medical College and Hospital Kishanganj for a tenure of 10 months (June 2021–March 2022). After initial clinical assessment, blood investigation was sent for various biochemical (C-reactive protein, complete blood count, and neutrophil lymphocyte ratio) and microbiological (D-dimer, COVID IgG) assessment to come to a diagnosis of MIS-C. Treatment protocol includes steroid (methyl prednisolone, dexamethasone) and in two cases IVIG. **Results**: Among all the 41 patients treated with steroid, 38 cases (92.7%) patient were successfully recovered and discharged. We also noticed there were significant neurological (39%), gastrointestinal (14.6%), and respiratory (24.4%) manifestation. We found association of coinfection with other organism among 3 cases (7.3%) among these 41 patients. **Conclusion**: MIS-C is a hyperinflammatory syndrome associated with SARS-CoV-2 in children and adolescents with fevers, shock, and multiorgan dysfunction. Steroids, IVIG, and aspirin are the first line of management. Refractory cases may need repeat doses of IVIG, steroids or immune-modulating drugs. However, in our study, we have demonstrated that most of the cases respond (92.7%) significantly to Methyl prednisolone alone.

Keywords: Children, COVID, Multisystem inflammatory syndrome in children, Steroid, Intravenous immunoglobulin

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Introduction

COVID 19 infection caused lot of morbidities and mortality globally. There were almost 4.4 million COVID-19 death reports by MPIDR COVERAGE database, about 0.4% (over 17,200) occurred in children and adolescent below 20 years of age. Of which 53% death occurred in adolescent belonging to age group of 10–19 years and 47% among children 0–9 years. Fortunately, the risk of infection and acute disease in children has been consistently low. Initially, no complications were noted in children. On May 1, 2020, the Royal College of Paediatrics and Child Health (RCPCH) reported cases with Paediatric Multisystem Inflammatory Syndrome (PIMS)-TS and enlightened us about the clinical management guidelines for children and proposed a case definition.[1]

These guidelines were formulated as health authorities at the UK (NHS) reported a number of seriously ill children with clinical signs of circulatory shock and/or hyperinflammatory states with features simulating Kawasaki disease (KD) or toxic shock syndrome. The same syndrome has been called multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. Some of these children were either tested positive for SARS-CoV-2 infection or had exposure to them from a positive contact.

During the peak of this COVID pandemic, a cluster of children had reported features similar to KD. They had fever, raised cytokine markers of inflammation and cardiac dysfunction. Soon, it was recognized that this set of severe symptoms with fever, severe inflammation, and associated multiorgan dysfunction was related to a separate entity with many features distinct from KD. This surge in cases, reported with a lag of few weeks following the peak. There was a temporal and consistent relationship in the rise of these cases with the rise in COVID-19 cases in the community.[2-4] Most of these children tested negative for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) but many showed positive anti-CoV-2 antibody responses(Anti COVID 19 IgG) speculating this syndrome to be a post-infective inflammatory response. These children presented with high-grade fever, multiorgan dysfunction often with shock

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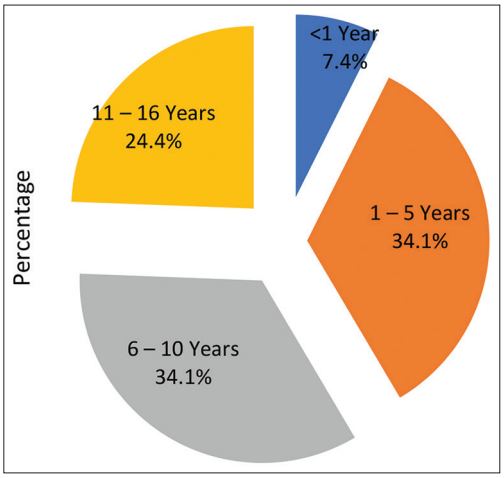

Figure 1: Age Distribution among study population

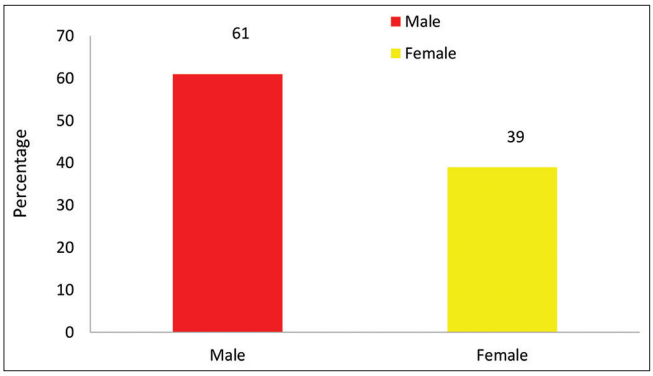

Figure 2: Sex distribution among study population

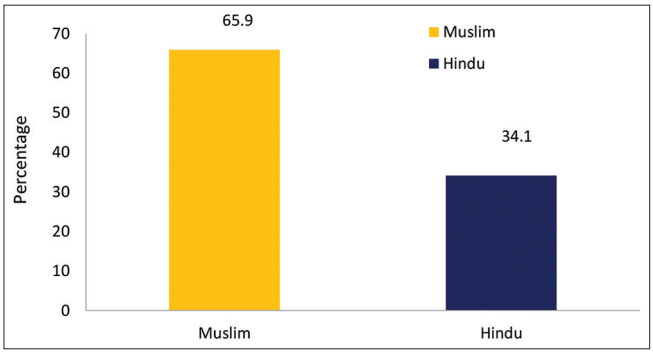

Figure 3: Distribution of religion (*n*=41)

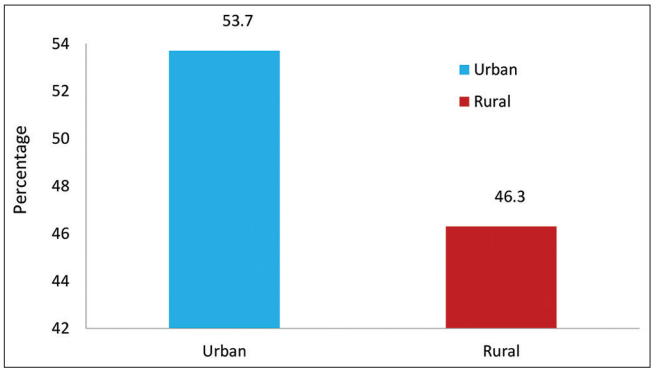

Figure 4: Distribution of area

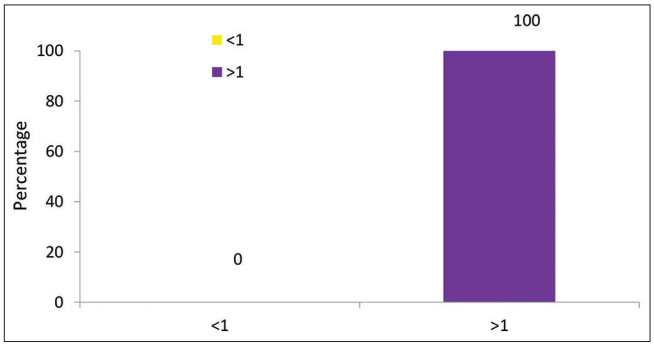

Figure 5: Serological investigation of COVID –IgG

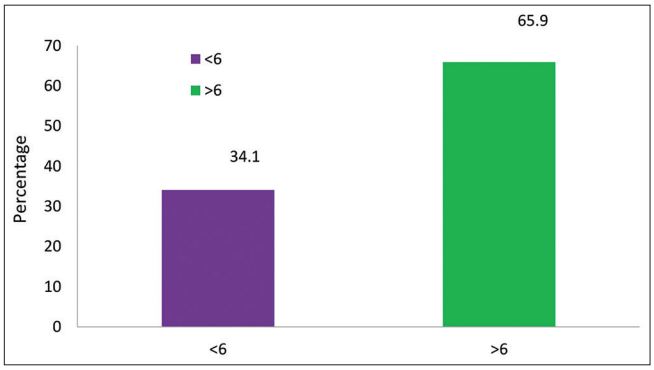

Figure 6: Serological investigation of CRP

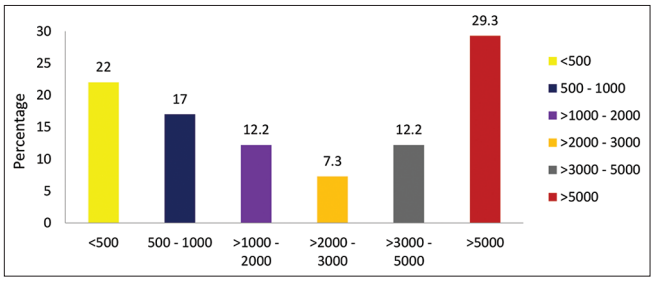

Figure 7: D- dimer among study population

and with features overlapping KD, KD shock syndrome, toxic shock syndrome, and macrophage activation syndrome.[5]

Clinical guidance generated was intended to take appropriate management fast but it was not meant to supplant clinical decision-making. Modifications and individualization of treatment plans, particularly in patients with complex conditions, were carried out to save lives of ailing children. The decision varied according to patient profile, geography, and availability of resources. Treatment with intravenous immunoglobulin (IVIG) has been a predominant management option. Methylprednisolone, heparin, and anti-inflammatory agents such as tocilizumab have also been tried. A few children with PIMS-TS have required inotropic support, mechanical ventilation, and extracorporeal membrane oxygenation.

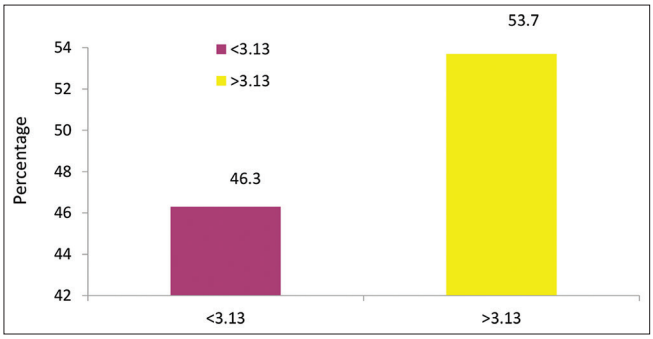

Figure 8: Hematological investigation of neutrophil lymphocyte ratio

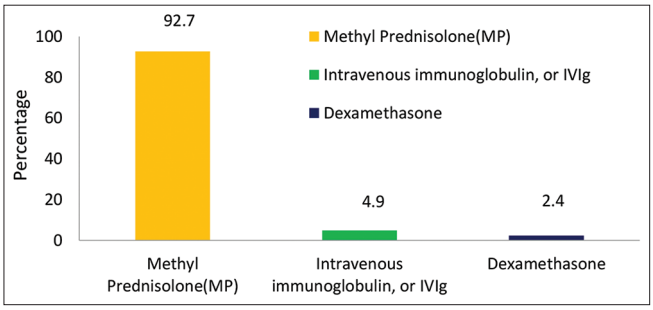

Figure 9: Treatment given among study population

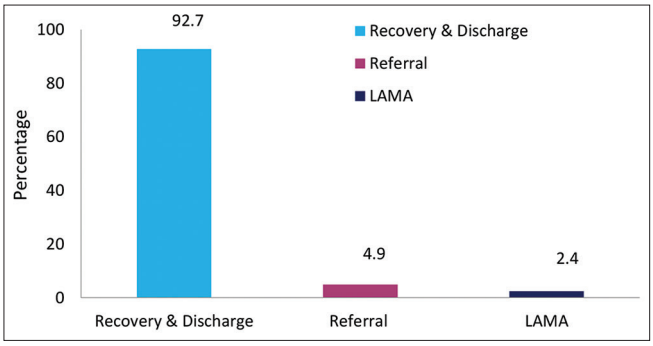

Figure 10: Final outcome

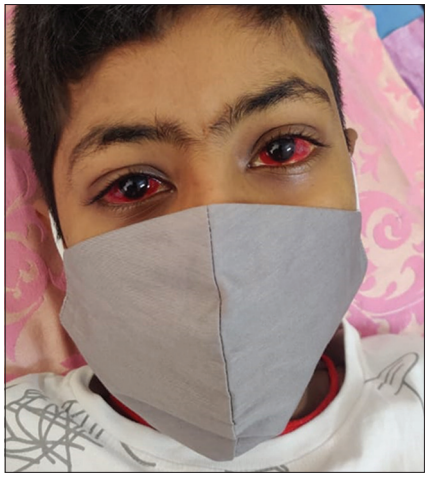

Figure 11: First case of MIS-C with subconjunctival hemorrhage[23]

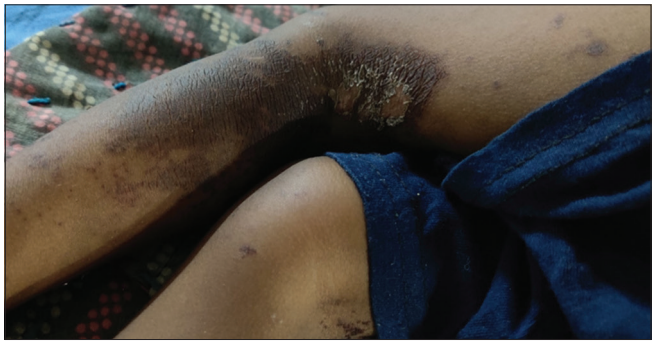

Figure 12: Extensive hyperpigmented plaque with exfoliation in a case of MIS-C[24]

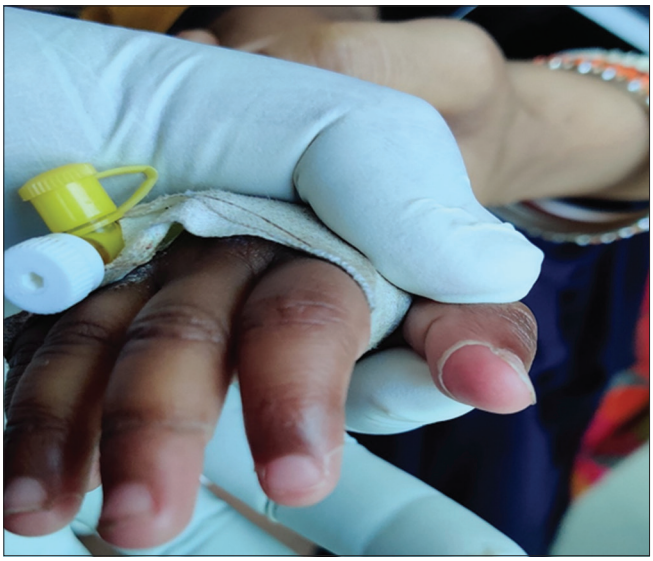

Figure 13: Erythema and subungual skin peeling in a child of MIS-C with Kawasaki like presentation[25]

We could not arrange IVIG in most of the cases (except 2 cases) for the financial constraints of the parents. So to save lives, we administered IV Methyl Prednisolone which came out to be savior.

Materials and Methods

Study Centre

The study was conducted at the Department of Pediatrics, Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital, a tertiary health care center in Kishanganj Bihar.

Study Group

Children and adolescent between 0–18 years.

Study Period

10 months (June 2021–March 2022).

Inclusion Criteria

(Fulfilling Diagnostic criteria of the WHO and DGHS)

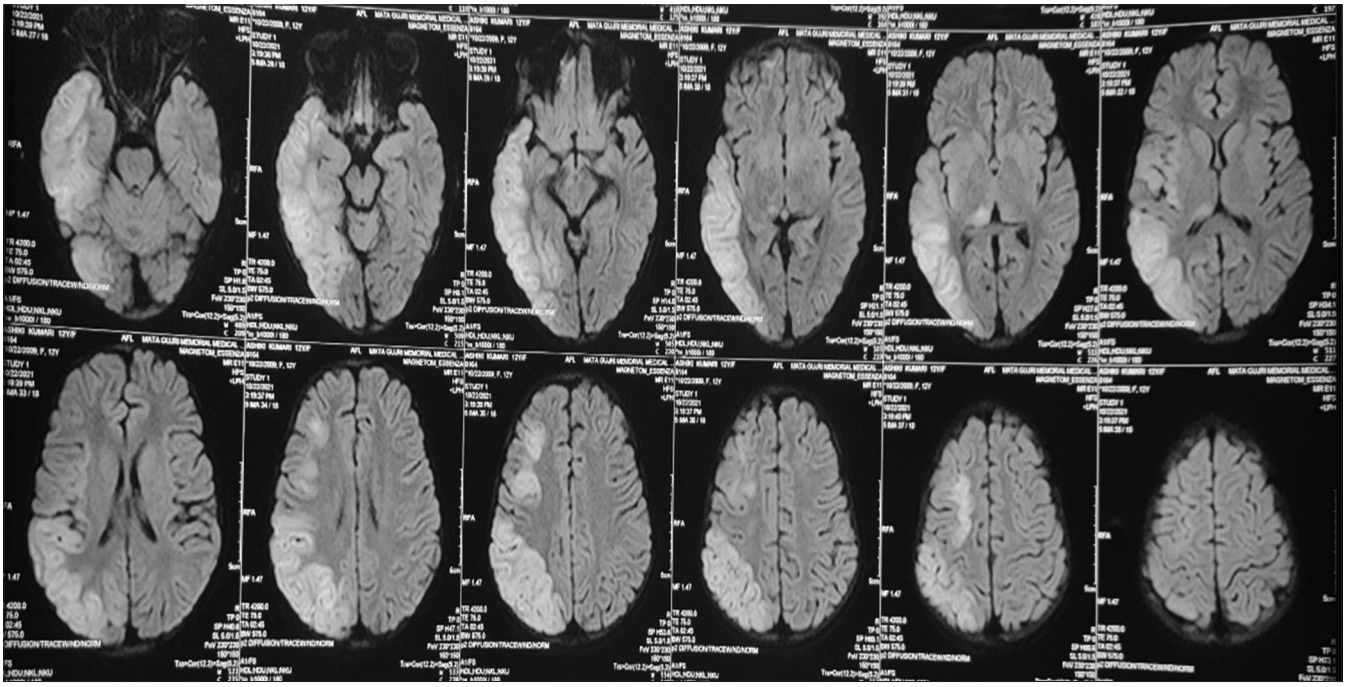

Figure 14: MRI brain showing ADEM like feature in MIS-C[26]

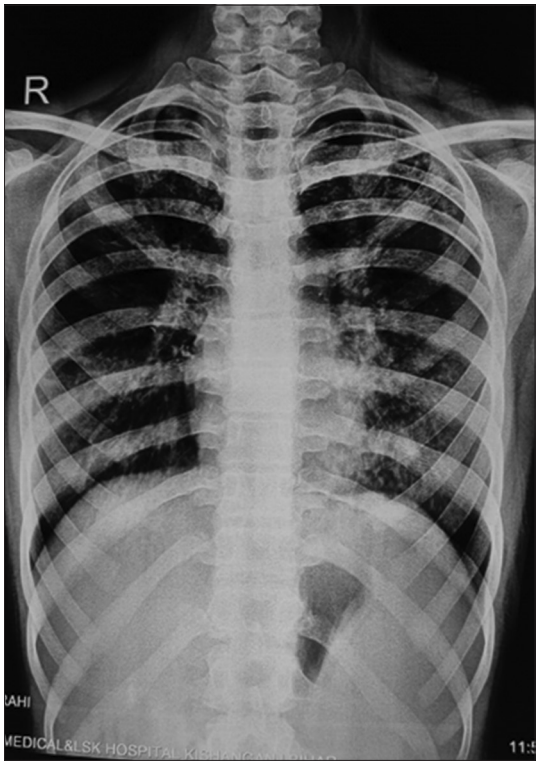

Figure 15: Miliary shadows in chest X-ray (posterior-anterior view) in a girl with MIS-C associated miliary tuberculosis[27]

Table 1: Age distribution among study population (*n*=41)

Age in year	*No of cases*	*Percentage*
<1 Year	03	7.4
1–5 Years	14	34.1
6–10 Years	14	34.1
11–16 Years	10	24.4
Total	41	100.0
Mean and SD Value	7.234±4.55	

Table 2: Sex distribution among study population (*n*=41)

Sex	*No of cases*	*Percentage*
Male	25	61.0
Female	16	39.0
Total	41	100.0
Ratio	M: F-1.56:1	

Table 3: Distribution of religion (*n*=41)

Religion	*No of cases*	*Percentage*
Muslim	27	65.9
Hindu	14	34.1
Total	41	100.0
Ratio	M: H-1.92:1	

Table 4: Distribution of area (*n*=41)

Area	*No of cases*	*Percentage*
Urban	22	53.7
Rural	19	46.3
Total	41	100.0
Ratio	U: R-1.15:1	

The following criteria were included in the study:

- Children and adolescents 0–18 years of age group presenting with fever ≥3 days(>38°C)
- After 2–4 weeks of recovery from acute COVID-19. infection
- And any two of the following:
- Rashes or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
- Hypotension and/or shock
- Features suggestive of myocardial dysfunction (poor left ventricular ejection fraction), pericarditis, valvulitis, or

coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)
- Evidence of coagulopathy (PT, PTT, and elevated D-Dimer >2000 ng/ml)
- Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)
- And elevated markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reactive protein, (CRP) Ferritin or procalcitonin
- And no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes and dengue
- And evidence of recent COVID-19 infection (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Exclusion Criteria

The following criteria were excluded from the study:
- Children and adolescent 0–18 year with fever <3 days
- Adolescents more than 18 years with fever
- Children presenting with isolated gastrointestinal problem such as recurrent pain abdomen, diarrhea, and pancreatitis
- Children with isolated neurological problem such as meningitis and encephalitis
- Children with isolated cardiological problem such as valvular and infective heart disease, cardiomyopathy, and arrhythmia
- Children presenting with isolated blood dyscrasia and coagulopathy
- Obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal, or streptococcal shock syndromes and dengue.

Ethical Approval and Informed Consent

Hospital ethics committee was informed about the study protocol. Informed consents were obtained from the parents of the study subjects after explaining to them in details the nature of the study.

Methodology

Pre-structured pro forma was used to record the information from the individual patient. After getting the consent from the parents' clinical data were collected and entered in the pro forma, include the age, sex, religion, presenting complaint, socioeconomic classes, comorbid illness (RTI, GIT infection, neurological deficit, hematological abnormality, skin changes, and others). After meticulous history taking and clinical examination, blood samples were collected from the patients for Complete blood count, inflammatory markers (CRP, ESR), D-Dimer, ferritin, and COVID IgG.

Statistical Analysis

All recorded data were analyzed with suitable diagrams, figures, tables and findings were discussed in details to draw appropriate conclusions using standard statistical analysis. Data were analyzed using Statistical Package for the Social Sciences Inc., Chicago, USA; Version 21.0.

Results

We have found in our study that most of the children were in the age group of 1 to 10 years [Figure 1] and [Table 1] with male preponderance 61% [Figure 2] and [Table 2]. Muslims suffered mostly at the tune of 65.9% [Figure 3] and [Table 3]. We found urban children suffered more from MIS-C (53.7%) [Figure4] and [Table 4] in comparison to rural children 9 46.3%. The children with MIS-C were suffering from fever,gastrointestinal disorders(19.6%); hematological (4.8%); neurological disorders(39%);respiratory disorders (24.4%) and cp-infections (7.3%) [Table5].We did Covid 19 IgG and all were positive [Figure 5] and [Table 6]. CRP were raised more than 6 mg/L in 65.9% children [Figure 6] and [Table 6]. D-Dimer value were raised more than 2000 ng/mL 48.8% children of our study. 29.3% had values more than 5000 ng/mL. [Figure 7] and [Table 8]. NLR (Neutrophlil Lymphocyte Ratio) were more than 3.13 (significant value) in 53.7% children [Figure 8] and [Table 9]. We treated 92.7% children with IV Methyl Prednisolone, 4.9% children with IVIG [Figure 9]and [Table 10]. The final outcome of treatment was very satisfactory as 92.7% became well and discharged home. 4.9% children were referred to higher center [Figure 10] and [Table 11]. We had one children with subconjunctival hemorrhage [Figure 11]. We also noted hyperpigmented skin lesions in one of our child [Figure 12]. We surprisingly noticed Kawasaki like disease with erythema and subungual skin peeling [Figure 13]. One of our MIS-C children had ADEM like features in clinical presentation and MRI Brain [Figure 14]. We got co infection in 3 out of 41 cases, 2 had Rickettial diseases and 1 with Miliary Tuberculosis [Figure 15].

Discussion

There are a growing number of media reports and publications from all corners of the World including India that a SARS-CoV-2-related inflammatory syndrome is emerging fast. PIMS-TS or MIS-C has high incidence of shock and myocardial involvement.[6,7] Our cases had similar features of multi-organ involvement including heart involvement detected by ECHO evidence as in two individuals, and gastrointestinal, hematological, or neurological involvement.[8]

Table 5 depicts clinical signs and symptoms of the patients. MISC patients generally have higher values of inflammatory markers such as CRP, neutrophil lymphocyte ratio, and d- Dimer.[7]

All our patients in the series had raised inflammatory markers. In accordance with the RCPCH, WHO, and CDC guidelines, common bacterial sepsis were excluded from the study. In all our patients, all cultures and common tropical infection mimics such as enteric fever, scrub typhus, and dengue were excluded from the study. Among 41 cases, we found 3 cases of co infections (2 with Rickettsial disease and 1 with tuberculosis).[9,10] Most of the published literature had either reverse transcriptase polymerase chain reaction positivity to COVID-19 virus or IgG antibody positivity or history of definite exposure to a positive case.[11]

PIMS-TS or MIS-C has been compared with KD but there are some differences such as an older age at presentation in former (mean age: 7 vs. 3 years in KD).[3] In our study, majority of cases fall in between 1 and 10 years (34.1%).

Among various manifestation of MIS-C, we report gastrointestinal manifestation (19.6%),[12] hematological (4.8%),[13] neurological (39%),[14,15] and respiratory (24.4.%).[16]

Fortunately, the approach of early recognition, prompt investigation, and appropriate therapy with treatments often used for

Table 5: Clinical signs and symptoms (*n*=41)

Signs and symptoms/No/%	*Variables*	*No of cases*	*Percentage*
Fever-41 (100.0%) with	Rash	4	9.8
	Shock	4	9.8
	Sub-conjunctival Hemorrhage (ITP)	2	4.9
Gastrointestinal disorders-8 (19.6%)	Pain abdomen	2	4.9
	Loose stool	4	9.8
	Skin changes with loose stool	1	2.4
	Conjunctival hemorrhage and abdominal pain (LVEF-42%)	1	2.4
Haematological Disorders-2 (4.8%)	Haematological (gum bleeding) and skin changes	1	2.4
	With pain abdomen and Gum Bleeding and subconjunctival hemorrhage	1	2.4
Neurological disorders- 16 (39.0%)	Meningitis	8	19.5
	Encephalopathy	3	7.3
	Encephalopathy with coinfection rickettsial infection	1	2.4
	ADEM	2	4.9
	Encephalitis	2	4.9
Respiratory disorder- 11 (24.4%)	Cough and breathing difficulty	9	21.9
	Empyema	1	2.4
	Hemoptysis (respiratory) with co-infection with pulmonary Koch (miliary tuberculosis)	1	2.4
	Respiratory difficulty with Pain abdomen	1	2.4
Shock with cardiological manifestation (LVEF -53%)		1	2.4
Shock with subconjunctival hemorrhage with Rickettsial coinfection		1	2.4
Signs and symptoms/No/%	*Variables*	*No of cases*	*Percentage*
Co-infection (7.3%)	Shock with subconjunctival hemorrhage with coinfection rickettsial infection	2	4.8
	Encephalopathy with coinfection rickettsial infection		
	Hemoptysis (respiratory) with co-infection with pulmonary Koch (Miliary tuberculosis)	1	2.4

Table 6: Serological investigation of COVID –IgG (*n*-41)

COVID- IgG	*Cutoff value*	*No of cases*	*Percentage*	*Mean and SD*
	<1	00	0.0	6.373±7.01
	>1	41	100.0	
Total		41	100.0	

Table 7: Serological investigation of CRP (*n*-41)

CRP	*Cutoff value*	*No of cases*	*Percentage*	*Mean and SD*
	<6	14	34.1	13.256±8.86
	>6	27	65.9	
Total		41	100.0	

Table 8: D- dimer among study population

D- dimer (ng/ml)	*Range (ng/ml)*	*No of cases*	*Percentage*	*Mean and SD*
	<500	9	22.0	2847.26 ± 3012.47
	500–1000	7	17.0	
	>1000–2000	5	12.2	
	>2000–3000	3	7.3	
	>3000–5000	5	12.2	
	>5000	12	29.3	
Total		41	100.0	

Table 9: Hematological investigation of neutrophil lymphocyte ratio

Neutrophil lymphocyte ratio	*Cut-off value*	*No of cases*	*Percentage*	*Mean and SD*
	<3.13	19	46.3	3.605±2.28
	>3.13	22	53.7	
Total		41	100.0	

KD had worked in MIS-C as well, with high rate of recovery. Nonetheless, the ideal and optimum treatment for MIS-C remains uncertain.

Table 10: Treatment given among study population (*n*-41)

Treatment given	*No of cases*	*Percentage*
Methyl prednisolone (MP)	38	92.7
Intravenous immunoglobulin	2	4.9
Dexamethasone	1	2.4
Total	41	100.0

Table 11: Final outcome (*n*=41)

Outcome	*No of cases*	*Percentage*
Recovery and discharge	38	92.7
Referral	02	4.9
LAMA (leave against medical advice)	01	2.4
Total	41	100.0
Length of hospital stay (days) 16.073±7.49		

The majority of patients in the literature have been treated with immunomodulatory therapy with IVIG, steroids, and fewer with anakinra, infliximab, or tocilizumab.[17,18] Patient with cardiac involvement requires aggressive therapy with ICU admission and early immunomodulation, as has been observed by Belhadjer *et al*.[19]

In our patient; however, we mainly used steroid Methylprednisolone 10–30 mg/kg for 5 days, then reducing doses over 4–6 weeks (for lack of affordability of costly IVIG) and IVIG in 2 cases with satisfactory outcome. None was administered Tocilizumab, Infliximab, and Anakinra. So steroid only treatment in MIS-C may be opted as treatment protocol if IVIG cannot be procured, particularly in less resourceful countries and poor section of our society.

The treatment provided by us is supported by reports from the scientific literature and recommendations from public health institutions.[20-22]

However, COVID-19 is still currently a new infection and as it unfolds its wings, newer treatment modalities will enlighten us. Further research is needed to understand immunobiology, spectrum, best therapy, and follow-up of such patients, particularly those involving the heart, and for this, multiple registries have been started by the WHO, RCPCH, and others.

Conclusion

MIS-C is an emerging emergency situation that first presented in April 2020 amid the global COVID pandemic. Based on initial reports from China, it was thought that children have a low incidence of symptomatic infection. However, the increased prevalence of MIS-C suggests a delayed hyperimmune response to SARS-CoV-2 infection in children. The exact incidence of MIS-C following an asymptomatic or mildly symptomatic infection with SARS-CoV-2 is not known. Further studies evaluating the predisposing factors and pathogenesis of MIS-C are warranted to appropriately prevent and optimally manage this condition. In this study of cases fulfilling the WHO criteria of MIS-C, we have characterized important clinical, biochemical, and radiological features of this novel syndrome.

In our institution among the rising number of cases of MIS-C from 2021 majority of children fall in between age group of 1–10 year with male predominance. Mostly they suffered from neurological complication (39%) followed by respiratory (24.4%) contrary to popular belief of gastrointestinal[28] and cardiological[29] complication. We also noticed significant co infection predisposition with Rickettsia (4.8%) and Miliary tuberculosis (2.4%). Majority of the patient is treated with steroid (95%) and IVIG (4.9%) with a recovery rate of 92.7%.

The limitation of this study was that it was a retrospective, single-center study. The sample size was small; therefore, the findings of this study cannot be generalized. Furthermore, we could not perform cytokine study which could be the determining factor of administration of monoclonal antibodies. This study data provide us with a foundation of the epidemiology and clinical manifestation of the novel syndrome of MIS-C in surrounding rural area of Bihar and its alternative remedy with steroid only treatment protocol.

Ethical Approval

The study was approved by the Institutional Ethics Committee.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In these forms, the legal guardians have given their consent for images and other clinical as well as investigational information to be reported in the journal. The guardians understand that names and initials will not be published.

Financial Support and Sponsorship

Nil

Conflicts of Interest

There are no conflicts of interest.

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