

Original Research Article

Ocular manifestations and clinical profile of multisystemic inflammatory syndrome in children during COVID-19 pandemic

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ABSTRACT

Background: Multisystemic inflammatory syndrome in children (MIS-C) is a new childhood disease, which is associated with Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The objective of the study was to evaluate ocular manifestations and clinical characteristics of MIS-C during COVID-19 pandemic.

Methods: A cross-sectional observational study was conducted among 48 MIS-C patients (≤19 years) at Burdwan Medical college and hospital in West Bengal, India from April 2021 to June 2021. History taking, clinical examination and necessary investigations of all the patients were done.

Results: Out of 48 patients, 18 patients (37.5%) presented with conjunctivitis, 4 (8.3%) with eyelid swelling, 2 (4.2%) with episcleritis, 2 (4.2%) with papilledema, 1 (2.1%) with subconjunctival haemorrhage, 1 (2.1%) with uveitis, 1 (2.1%) with retinitis and 4 (8.3%) with decreased vision. Other clinical manifestations included fever, skin rash, loose stool, vomiting, abdominal pain, cough, peripheral oedema, myalgia, breathlessness, altered sensorium, cervical lymphadenopathy, shock, oliguria, chest discomfort and joint swelling. Serum inflammatory, coagulation and cardiac markers were deranged.

Conclusions: Ocular and other clinical manifestations in MIS-C were due to post-COVID immuno-dysregulation resulting in “cytokine storm” and hyper-inflammatory response. Conjunctivitis was the most common ocular manifestation. There was a positive correlation between severity of the conjunctival hyperaemia and level of serum inflammatory markers.

Keywords: MIS-C, COVID-19, Conjunctivitis

INTRODUCTION

Multisystemic Inflammatory Syndrome in Children (MIS-C) is a new childhood disease, which is associated with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). MIS-C is also known as Pediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS). It appears to be a delayed, post-infectious complication of COVID-19 infection. Like adult, COVID-19 has many short term and

long term impact on health of children and adolescent. MIS-C has both ocular and systemic effects.

It may be dangerous and potentially lethal.¹ Both WHO and CDC gave the definition of MIS-C.^{2,3} Our study aimed at evaluation of ocular manifestations and clinical profile of patients with MIS-C during COVID-19 pandemic, also to study the correlation between the severities of conjunctival hyperaemia with serum inflammatory markers.

METHODS

A descriptive observational study of two months duration (April 2021 to June 2021) was conducted among 48 MIS-C patients (≤ 19 years) at a tertiary care centre in West Bengal, India. The admitted patients at paediatric and general medicine department, who were diagnosed as MIS-C were selected.

Inclusion criteria for patient selection was: patients ≤ 19 years old, with fever $>38^{\circ}\text{C}$ for >3 days, with multi-system (>2) involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); with elevated serum inflammatory markers (ESR, CRP, LDH, IL-6, ferritin), with no other systemic infection by microbial organisms; and evidence of COVID-19 by Rapid antigen test (RAT), Real time reverse transcription polymerase chain reaction (RT-PCR), IgG antibody titre or history of contact with patients with COVID-19 within the four weeks prior to the onset of symptoms. To confirm the evidence of COVID-19 infection. In case of negative RTPCR, COVID-19 antibody (IgG) titre was done. Patients with RAT+, RTPCR+, RTPCR negative but positive for antibody titre, positive contact history with COVID-19 patients were included in our study. Children with Kawasaki disease, toxic shock syndrome and macrophage activation syndrome were excluded from the study.

Data was collected by taking history, examining the patients and doing necessary blood and radiological investigations. Among ocular examination, visual acuity was assessed by using ETDRS chart, Snellen acuity chart, E chart, Cardiff acuity cards and Teller's acuity chart; extra-ocular examination and pupillary light reaction was tested by torch light; anterior segment examination was done by using slit lamp fundus examination was done by indirect ophthalmoscope. Post-segment was assessed by OCT, USG-B scan whenever indicated. Among blood investigations, complete blood count, serum inflammatory markers, coagulation profile, cardiac markers, liver function test, kidney function test, serum lipase and amylase were done. Echocardiography, MRI brain and orbit, chest X-ray and USG-abdomen were done whenever indicated. We categorized the patients according to age into three groups of 5-12 years and 13 to ≤ 19 years. We used the (Japan Ocular Allergy Society) grading system to categorize the conjunctival hyperemia into four grade (0-no vessel dilatation, 1-some vessels dilatation, 2-extensive vasodilatation, 3-overall vasodilatation).⁴ The data were collected in a case record format and analysed using cross tabulation and diagram and finally entered on a Microsoft Excel spreadsheet. Institutional ethics committee approval was taken. Written consent from the patients was taken.

RESULTS

The study was conducted among 48 patients with MIS-C and majority (50%) of them were below 5 years (Table

1). Median age group affected was 8.1 years. Out of 48 patients, 28 patients (58.3%) were males and 20 patients (41.7%) were females (Table 2).

Table 1: Age distribution of MIS-C patients.

Age (in years)	Number	Percentage
0 to 5	24	50
5 to 12	18	37.5
12 to ≤ 19	6	12.5

Table 2: Sex distribution of MIS-C patients.

Sex	Number	Percentage
Male	28	58.3
Female	20	41.7

During the evaluation of evidence of COVID-19 infection, we found that 36 patients (75%) had antibody positive, patients (15%) RNTCP positive, 4 patients (8%) had positive history of contact with COVID-19 patients and 1 patient (2%) was rapid antigen positive (Figure 1).

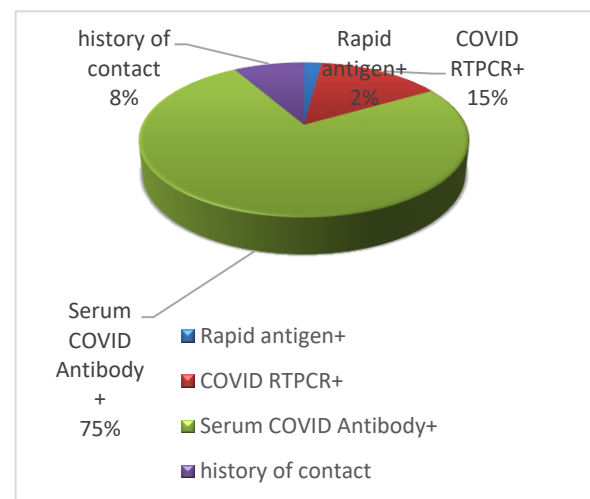


Figure 1: COVID-19 serology status of the children with MIS-C.

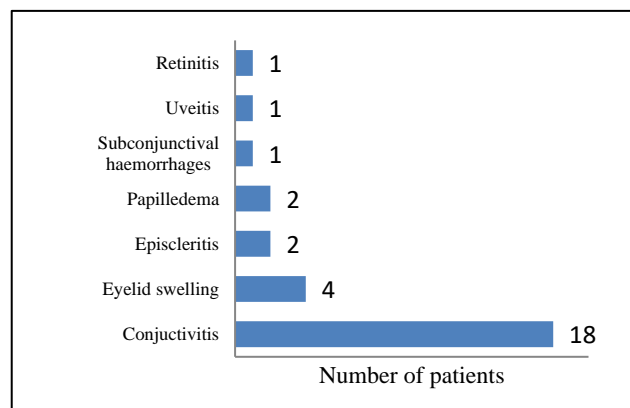


Figure 2: Ocular manifestations in patients with MIS-C.

During ocular examination, we found that out of 48 patients, 18 patients (37.5%) presented with conjunctivitis (most common ocular finding), followed by 4 patients with eyelid swelling (8.3%), 2 with episcleritis (4.2%), 2 with papillaedema (4.2%), 1 with subconjunctival haemorrhages (2.1%), 1 with uveitis (2.1%), 1 with retinitis (2.1%). 4 patients (8.3%) presented with decreased vision (Figure 2).

General and systemic examination revealed that all 48 patients presented fever, which was most common general manifestation followed by skin rash in 32 patients (66.7%), loose stool in 28 patients (58.3%), vomiting in 28 patients (58.3%), cough in 20 patients, myalgia in 12 patients (25%), breathlessness in 6 patients (12.5%), chest pain in 6 patients (12.5%), altered sensorium in 5 patients (10.4%), cervical lymphadenopathy in 5 patients (10.4%), peripheral oedema in 4 patients (8.3%), shock in 3 patients (6.25%), oliguria in 2 patients (4.2%), joint swelling in and 1 patients (2.1%) (Figure 3).

Blood investigation showed that mean total leucocyte count (13,346 cells/cumm) was above the normal.

All inflammatory markers were deranged (mean level of ESR 46.7 mm 1st hour, CRP 40.4 mg%, IL-6 2866.4 pg/ml, 1154.6 IL/ml, Ferritin 436.9 ng/ml). Coagulation profile (mean level of PT 15.3 sec, INR 1.23, APTT 47.8 sec, D-dimer level 6.52 microgram/ml) was also deranged. Mean value of liver function test (LFT), urea and creatinine was normal, but altered in few patients who developed inflammatory damage to hepatocytes or acute kidney injury (AKI) (Table 3).

We categorized the patients into 4 groups with respect to CRP level (Group 1: 6-25 mg%, Group 2: 26-45 mg%, Group 3: 46-65 mg%, Group 4: 66-90 mg%). In each group, there are blue, brown and green box represents grade 1, 2 and 3 conjunctival hyperaemia respectively. As the CRP level increases, number of patients with higher grading also increases (Figure 4).

All 48 patients treated with IV Methylprednisolone, 36 patients with IVIG, 12 patients with aspirin, 6 patients with s/c enoxaparin, 4 patients with inotrope support and mechanical ventilation, 2 patients underwent hemodialysis.

Table 3: Blood parameters in MIS-C patients.

Investigations	Value (range)
Hb%	9.9 (7.9-12.5) g%
TLC	13,346 (4900-30,200) cells/cumm
DLC	
Neutrophils	56.1 (30-80) cells/ μ l
Lymphocytes	34.3 (13-63) cells/ μ l
Platelet	197,750 (85000-318,000)/cumm
ESR	46.7 (22-102) mm Hg 1 st hour
CRP	40.4 (6.2-86.7) mg%
IL-6	2866.4 (22.3-5500) pg/ml
LDH	1154.6 (658-2504) IU/ml
Ferritin	436.9 (39.8-1226.80) ng/ml
Coagulation profile	
PT	15.3 (13.1-18.3) sec
INR	1.23 (1.09-1.46)
APTT	47.8 (30.9-57.5) sec
D-dimer	6.52 (0.18-8.27) μ g/ml
CPK	670 (46-4343) IU/ml
CPK-MB	64.5 (10-274) IU/ml
LFT	
Total bilirubin	0.69 (0.6-0.8) mg%
Unconjugated bilirubin	0.3 (0.2-0.4) mg%
Conjugated bilirubin	0.39 (0.2-0.6) mg%
SGOT	49.7 (22-84) U/l
SGPT	58.8 (25-104) U/l
Alkaline phosphatase	171.7 (101-296) IU/l
Total protein	6.51 (6.0-7.1) g%
Albumin	3.54 (2.9-4.0) g%
Globulin	3.03 (2.8-3.2) g%

Continued.

Investigations	Value (range)
Urea	26.8 (18-142) mg%
Creatinine	1.2 (0.6-3.7) mg%
Serum lipase	45 (25-62) U/l
Serum amylase	62 (22-74) U/l

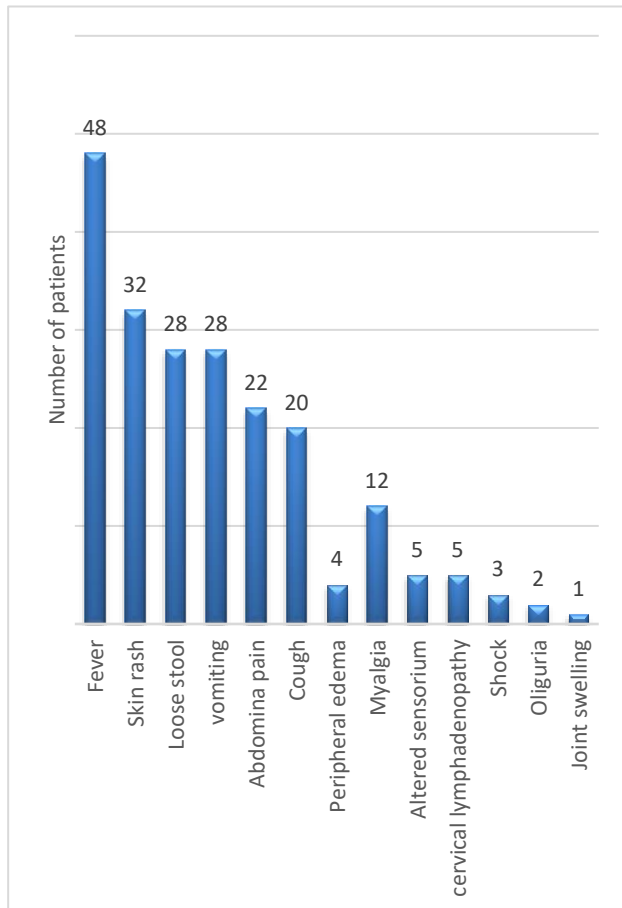


Figure 3: General and systemic manifestations in patients with MIS-C.

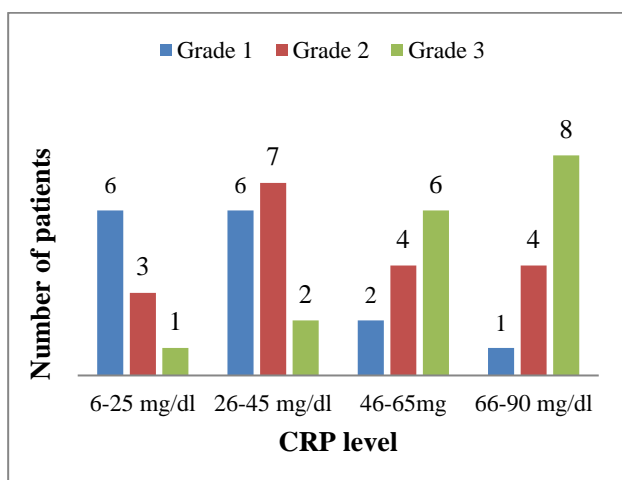


Figure 4: Correlation between severity of ocular manifestations and CRP level.



Figure 5: Redness, watering, conjunctival vessels congestion in a MIS-C patient; (b) episcleral vessels congestion in inferotemporal aspect in a patient with MIS-C; and (c) sub-conjunctival haemorrhage in a MIS-C patient involving both the eyes.

Among ocular treatment, for conjunctivitis, topical NSAIDs (Ketorolac) and topical antibiotic (to prevent secondary bacterial infection) eye drops were given; for uveitis, topical steroid (prednisolone acetate/dexamethasone) and cycloplegic (atropine/homatropine) eye drops were given; for subconjunctival hemorrhage, topical NSAIDs and artificial tear drops were given; For eyelid swelling and retinitis, no specific ocular treatment was given as patients are on systemic steroid; for papilledema, neuroprotector (Tab. Methylcobalamine 1500 mcg) and ICT lowering drugs (IV mannitol/Tab. Diamox) were given.

DISCUSSION

MIS-C is related to immune dysregulation occurring after acute COVID-19 infection has passed.^{5,6} It is a hyper-inflammatory condition, and most of the manifestations occur as a result of “cytokine storm”. Consiglio CR suggested multiple autoantibodies that could be involved in the pathogenesis of MIS-C.⁷ Transmission of the infection occurs through ocular surface via ACE-2 receptors and TMPRSS2 demonstrated on conjunctival and corneal epithelium.⁸

During patients selection, we the cut off age (≤ 19 years) of the WHO criteria for MIS-C. Patients with Kawasaki disease or toxic shock syndrome or macrophage activation syndrome are excluded from our study, as they have similar clinical presentation of MIS-C.

In our study, it was found that majority (50%) of the patients are below 5 years (Table 1), with median age group affected was 8.1 years, which is similar to the result of study by Feldstein et al.⁹ Males (53.3%) were more commonly affected than females (47.7%). COVID-

19 serology status had shown majority of the patients are COVID-19 antibody (IgG) positive followed by RT-PCR positive, history of contact with COVID-19 patients, which suggested that MIS-C after active infection. This is similar to the study done by Dhanalakshmi et al where low incidence of RT-PCR positivity with high presence of SARS-CoV-2 antibodies in MIS-C patients was found.¹⁰

Previous studies had shown ophthalmic manifestations of COVID-19 ranges from conjunctivitis, episcleritis, central retinal venous occlusion (CRVO), central retinal artery occlusion (CRAO), neuroretinopathy, maculopathy, vitritis, acute retinal necrosis (ARN), retinal haemorrhages, serpiginous choroiditis, papillophlebitis, optic neuritis, cranial nerve palsies, neurogenic ptosis, dacryadenitis, orbital cellulitis, rhino-orbital mucormycosis.¹¹⁻¹³

Danthuluri et al reported conjunctivitis in MIS-C patient.¹⁴ In our study, the most common ocular manifestation of MIS-C was conjunctivitis (Figure 5a). We did not do the RTPCR of the tear film to rule out whether the conjunctivitis is due to infection caused by the other microbial organisms or inflammatory due to the hyper-inflammatory damage by the COVID-19 infection. This is because the immunopathogenesis and clinical presentation of MIS-C is different from adult patient with COVID-19 active infection. So, if we clinically suspected that the conjunctivitis was caused by inflammatory response, then only we included them.

As the CRP level increases, number of patients with higher grading also increases (Figure 4), which suggests a positive correlation between CRP level and severity of conjunctival hyperaemia grading.



Figure 6: Fundus photo of a MIS-C patient showing grade 1 papilledema (disc margin blurring with temporal pallor).

Eyelid swelling was the second most common ocular manifestation. Patients presented with episcleritis which was also due to inflammatory response of the episcleral tissue (Figure 5b). 1 patient presented with bilateral subconjunctival haemorrhages (Figure 5c). This might be due to inflammatory damage to the conjunctival vessels wall or alteration of coagulation profile secondary to inflammatory damage to liver hepatocytes or secondary to anticoagulant use as a part of treatment.

Gupta et al reported MIS-C with scrub typhus infections.¹⁵ We also found 2 cases of MIS-C with scrub typhus meningitis and they all developed papilledema due to increased ICT secondary to meningitis. Bettach et al. and Öztürk et al. reported bilateral anterior uveitis in a MIS-C patient.^{16,17} We also found 1 case of anterior uveitis in a MIS-C patient. 8.3% patients presented with decreased vision, which was due to uveitis, retinitis and long standing papilledema.



Figure 7: Systemic manifestations in patients with MIS-C (a) erythematous skin rashes; (b) ankle joint swelling; (c) non-pitting oedema over hand; and (d) shows right coronary artery ectasia in a MIS-C patient (Z-score of 2.11).

MIS-C is a multisystem inflammatory disease and has impact on different systems.¹⁸⁻²⁵ In our study, we also found all the systems involvement (Figure 7).

5 patients presented with chest pain and were diagnosed as myocarditis. 3 patients (6%) out of them were developed heart failure and shock, whereas the study conducted by Whittaker et al patient developed shock.²⁴ Few patients were developed coronary ectasia, pericardial effusion and myocarditis. Similar result also found in the study conducted by Matsubara et al. among US children for echocardiographic changes in MIS-C.²⁵

Literature showed there are very few studies were done on ocular manifestations in MIS-C patient. To our best

knowledge, our study has shown different ocular manifestations in details for the first time.

Limitation

Few patients did not afford the cost of Covid-19 antibody test and they were excluded from our study. As there were very few studies done on ocular manifestations in MIS-C patient, we did not find enough data during literature review were the limitation of the study.

CONCLUSION

MIS-C may cause ocular and other clinical manifestations and alteration in blood parameters, due to post-covid immune-dysregulation, resulting in “cytokinin storm” and hyperinflammatory response. Among ocular finding, conjunctivitis was the most common finding. MIS-C is a new disease entity, hence needs further more study to evaluate and manage the ocular manifestations and clinical profile of the disease.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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