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Original Article

Clinicopathological and Laboratory Findings in the Cases of MIS-C in a Tertiary Care Hospital

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respirator syndrome coronavirus 2 (SARS-CoV-2) has affected almost all the countries, overwhelming the health-care system, causing significant mortality. Multi-system inflammatory syndrome in children (MIS-C) is a rare complication that appears to be linked to COVID-19 and develops as a result of an, as yet, unspecified immune dysregulation with an excessive inflammatory response.

Aims: The aim of the study was to assess and evaluate clinical, pathological, and laboratory findings and treatment outcomes among 15 MIS-C patients using electronic medical records.

Result: The 15 children ranged in age from 4 to 17 (median age 8.8), 12/15 were boys and all them came from different parts of the state. The most commonly involved organ systems were the gastrointestinal (15/15), hematologic (14/15), cardiovascular (15/15), skin and mucosa (15/15), and respiratory (12/15) ones. The estimated median duration of fever was 7 (IQR 5.75–7.25) days. All patients exhibited skin and mucocutaneous lesions. Maculopapular rash (11/15), cracking and hyperemia of lips (12/15), conjunctival injection (10/15), swelling and hyperemia of hands and feet (5/15), oral mucosal changes (11/15), and periorbital edema (11/15) were among the most common findings In addition. All 13 patients had acute gastrointestinal symptoms on admission, including abdominal pain (11/15), vomiting (10/15), and diarrhea (7/15).

Conclusion: During the current pandemic, every child with a fever should have a clearly defined epidemiological history of COVID-19, a careful clinical assessment of possible multiple organ-system involvement, with a special focus on children with severe abdominal pain and/or skin and mucocutaneous lesions.

Key words: Coronavirus disease 2019, Multi-system inflammatory syndrome in children, Severe acute respirator syndrome coronavirus 2

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has affected almost all the countries, overwhelming the health-care system, causing significant mortality. Initial reports worldwide showed that most children are asymptotic or have mild-to-moderate disease.

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We, in our institute Burdwan Medical College and Hospital, have conducted a study on the patients of multi-system inflammatory syndrome in children (MIS-C) admitted our institute over a period of 8 weeks (May 2022–July 2022) and have described their clinical features, laboratory parameters, treatment modalities, and outcome in the following study.

Criteria of MIS-C

The centers for disease control and prevention have declared MIS-C to be a reportable illness as of May 14, 2020. The Health and Family Welfare Department, Government of West Bengal has recently provided a diagnostic criterion of MIS-C which includes patients with age between 0 and 19 years, fever for more than equal to 3 days, clinical signs of multi-system involvement (at least 2 of the following – mucocutaneous, cardiac, hypotension, shock,

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coagulopathy, acute gastrointestinal symptoms), elevated markers of inflammation (e.g. ESR, CRP, Pro-calcitonin), no other obvious microbial cause of inflammation, and evidence of SARS-COV-2 infection (Any one of the following – Positive SARS-CoV-2 RT- PCR, Positive serology, Positive Rapid Antigen Test, and Contact with an individual with COVID-19). All six criteria must be met to fulfill the case definition of MIS-C. Based on the initial signs, symptoms and laboratory parameters, MIS-C has been grouped into three types: (1) MIS-C with febrile inflammatory state; (2) MIS-C with predominant Kawasaki like features; and (3) Severe MIS-C/MIS-C with shock.

Pathogenesis

The possible pathogenesis suggested for the development of MIS-C is immune mediated injury resulting in a hyperinflammatory state and inflammatory vasculopathy. Thus, clinical features delineated from studying several cases worldwide show overlapping features with Kawasaki Disease (KD), Toxic Shock Syndrome, KD Shock Syndrome, and Macrophage Activation Syndrome. Multiple reports of pediatric inflammatory multi-system syndrome temporally associated with SARS-CoV-2 (PIMS-S), MIS-C, KD, and Kawasaki-like syndrome were published from the countries with high case load of COVID-19 like the UK, France, Italy, and the United States of America describing the demographic details, clinical features, investigations, treatment details, and outcome.

Following the World Health Organization's announcement on March 11, 2020, that the spread of the novel coronavirus (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had reached the scale of a global pandemic, the Latvian government announced a national state of emergency on March 12 to slow the spread of the disease in the country. In 2020, Latvia had a total population of 1.908 million and by March 2021 SARS-CoV-2 infection had been confirmed in 4.8% of the total population (90,997 individuals), of whom only 8.7% (7883) were children under 19 years of age.[1] Most of the children had a mild or moderate course of the disease and were treated at home, but 83 patients had more severe manifestations, necessitating hospitalization at Riga Children's Clinical University Hospital.

MIS-C is a rare complication that appears to be linked to COVID-19 and develops as a result of an, as yet, unspecified immune dysregulation with an excessive inflammatory response.[2] Several reports have suggested that children could still develop MIS-C despite an asymptomatic and mild course of SARS-CoV-2.[3,4] The definition of MIS-C is based on the following principal elements: Age, presence of fever, increased levels of

Table 1: Demographic and clinical characteristics of all 13 patients with multi-system inflammatory syndrome in children

Characteristic	Total
Sex, *n*	
Female	3/15
Male	12/15
Age in years, range, median	4–17, 8.8
Comorbidities, *n*	5/15
Days in hospital, median (IQR)	12 (11–18)
Outcome	Recovery
PICU admission, *n*	7/15
Days in PICU, median (IQR)	2 (1.25–2.75)
Clinical characteristic	
Duration of symptoms at admission, median days (IQR)	5 (4–6)
Days with fever, median (IQR)	7 (5.75–7.25)
Number of organ systems involved, *n*	
2–3	0/15
4–5	15/15
≥6	0/15
Clinical manifestations, *n*	
Fever	15/15
Rash	
Maculopapular	11/15
Petechiae	4/15
Mucocutaneous lesions	
Cracking/hyperemia of lips	12/15
Strawberry tongue	4/15
Oropharyngeal erythema	8/15
Conjunctival injection	10/15
Extremity changes	
Swelling/hyperemia of hands and feet	5/15
Cervical lymphadenopathy >1.5 cm D	8/15
Gastrointestinal	
Abdominal pain	11/15
Ileus	5/15
Vomiting	10/15
Diarrhea	7/15
Cardiovascular	
Hypotension	5/15
Tachycardia	15/15
Myocarditis	2/15
Congestive heart failure	3/15
Cardiac dysfunction	10/15
Respiratory	
Cough	12/15
Shortness of breath, tachypnea	3/15
Desaturation	6/15
Chest pain	2/15
Pneumonia	7/15
Pleural effusion	9/15
Neurologic	
Headache	6/15
Dizziness	3/15
Meningism/photophobia	5/15
Hyperesthesia	2/15
Emotional lability	4/15
Unsteady gait	2/15
Other	
Periorbital edema	11/15
Skin peeling of hands and feet	2/15
Hepatomegaly	6/15
Splenomegaly	4/15

IQR: Interquartile range, PICU: Pediatric intensive care unit

Table 2: Laboratory values and radiographic findings in the patients with multi-system inflammatory syndrome in children

Characteristic	Results The median of peak values (IQR)
Initial laboratory criteria, (reference ranges)	
CRP (0–5) mg/L	183.04 (135.65–241.09)
ESR (0–15) mm/h	45 (40.7–65.3)
Lymphopenia (0.97–4.28) (10^3 μL)	0.55 (0.44–0.65)
Thrombocytopenia (175–369) (10^3 μL)	112 (94–131.20)
Hyponatremia (132–145) mmol/L	125.60 (125.9–130.29)
Hypoalbuminemia, (38–54) g/L	24.19 (24.1–30.14)
Additional inflammatory markers	
IL-6 (0–2) pg/mL	190 (149–330)
Ferritin (20–200) ng/mL	580.5 (511.5–860.1)
LDH (120–300) U/L	330 (325.79–342.27)
Cardiac biomarkers	
NT-Pro BNP (0–125) pg/mL	7219 (2432–17130)
Troponin (0–19) ng/mL	93.5 (46.5–131.3)
Coagulation parameters	
D-dimer (0–0.55) (mg/mL)	5.95 (3.30–10.50)
Fibrinogen (1.7–4.2) (mg/dL)	5.69 (4.80–7.04)
Chest X-ray	
Interstitial edema/thickening	6/15
Pleural effusion	2/15
Inflammation	4/15
Bronchial obstruction, drainage disorder	5/15
Enlarged heart	2/15
Electrocardiography	
Various changes of ST-segment or T-wave	13/15
Bradyarrhythmias	8/15
Tachyarrhythmias	8/15
Intraventricular conduction defects	12/15
AV dissociation	1/15
Echocardiography	
Valvular insufficiency	
Mitral	9/15
Tricuspidal	8/15
Aortal	5/15
Pulmonal	1/15
Pericardial effusion	4/15
Decreased LV ejection fraction	6/15
RV, RA dilatation	1/15
Abdominal ultrasonography	
Ascites	2/15
Hepato- and/or splenomegal	4/15
Mesadenitis	3/15
Renal parenchymal changes, cystitis	5/15
Pericholecystitis	1/15
Effusion in the abdominal cavity/pelvis	3/15
Pleural ultrasonography-effusion	9/15
Computed tomography of the lungs	
Bilateral polysegmental pneumonia	2/15
Fibrotic changes	2/15
Cardiac magnetic resonance-myocarditis	1/15
SARS-CoV-2 test results at the admission	
Positive nasopharyngeal RT-PCR	0–15
Positive serology	15–15
History of COVID-19 (+) contact	15–15

IQR: Interquartile range, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IL-6: Interleukin 6, LDH: Lactate dehydrogenase, SARS-CoV-2: Severe acute respirator syndrome coronavirus 2

inflammatory markers, the involvement of more than two organ systems, temporal relation to COVID-19 infection or exposure, and exclusion of other diagnoses.[5] All 13 had documented fever >38.0°C for ≥24 h at the time of presentation, severe illness involving more than two organ systems, and laboratory evidence of inflammation; equally, they all were linked to SARS-CoV-2 infection.

Aims and Objective

The aim of the study was to assess and evaluate clinical, pathological, and laboratory findings and treatment outcomes among 15 MIS-C patients using electronic medical records.

RESULTS

Clinical and pathological findings in MIS-C patients [Table 1] developed 2–6 weeks after acute illness or contact with a COVID-19 positive person in all 15 patients, and they were hospitalized on the 3rd–7th day of illness (median five, interquartile range [IQR] 4–6 days). Only five patients out of the 15 were symptomatic during the acute COVID-19 phase; four had mild symptoms (subfebrility, cough, anosmia, and loss of taste), while one had a severe course of the disease and was admitted to hospital before the onset of MIS-C. The 15 children ranged in age from 4 to 17 (median age 8.8), 12/15 were boys and all them came from different parts of the state. Overall, 11/15 patients had no reported underlying medical conditions; one had bronchial asthma, another had autism spectrum disorder (ASD), while another had gallstone disease. The patient with ASD is the one who had a severe course of acute COVID-19.

Initial signs and symptoms of all study patients had a documented fever >38.0°C for ≥24 h at the time of presentation and severe illness involving at least four organ systems. The most commonly involved organ systems were the gastrointestinal (15/15), hematologic (14/15), cardiovascular (15/15), skin and mucosa (15/15), and respiratory (12/15) ones.

The estimated median duration of fever was 7 (IQR 5.75–7.25) days. All patients exhibited skin and mucocutaneous lesions. Maculopapular rash (11/15), cracking and hyperemia of lips (12/15), conjunctival injection (10/15), swelling and hyperemia of hands and feet (5/15), oral mucosal changes (11/15), and periorbital edema (11/15) were among the most common findings. In addition. All 13 patients had acute gastrointestinal symptoms on admission, including abdominal pain (11/15), vomiting (10/15), and diarrhea (7/15). Two patients underwent diagnostic laparoscopy –

one with an acute ileus and another with suspected acute appendicitis. Respiratory symptoms occurred in 12 patients overall, including a cough (12/15), acute respiratory distress with shortness of breath and tachypnea (9/15), desaturation episodes (6/15), and chest pain (2/15). Neurologic symptoms were present in (12/15) and acute cardiovascular manifestations in all 15 study patients. Five patients were hypotensive at the time of admission.

Laboratory markers and additional diagnostics initial laboratory criteria for strongly suspected MIS-C (9) as elevated C-reactive protein (CRP) ≥30 mg/L and/or erythrocyte sedimentation rate (ESR) >40 mm/h plus lymphopenia <1000 or thrombocytopenia <150 × 10^3 or hyponatremia <135 mmol/L were met in all 15 MIS-C patients. CRP was elevated in all 15 cases, median 183.04 (IQR 135.65–241.09) mg/L, elevated ESR in 12/15 patients, median 45 (IQR 40.7–65.3) mm/h, lymphopenia in 13/15 cases, median 555 (IQR 440–650) μL, thrombocytopenia in 12/15 cases, median 112 (IQR 94–131.20) μL, and hyponatremia in 9/15, median 125.60 (IQR 125.9–130.29) mmol/L.

Additional laboratory evidence of inflammation included increased serum ferritin with median 580.5 (IQR 511.5–860.1) ng/mL and serum cytokine interleukin 6 (IL-6) 190 (IQR 149–330) mg/L in all 15 cases. Lactate dehydrogenase was elevated in 9/15 patients with a median 330 (IQR 325.79–342.27) μ/L. Hypoalbuminemia was observed in 15/15 cases, median value 24.19 (IQR 24.1–30.14) g/L. All 15 patients had increased coagulation marker D-dimer, median 5.95 (IQR 3.30–10.50) mg/L, and fibrinogen in 8/15, median 5.69 (IQR 4.80–7.04) g/L. Blood tests also revealed elevated levels of cardiac troponin I in 9/15 patients with a median of 93.5 (IQR 46.5–131.3) ng/mL and N-terminal pro B-type natriuretic peptide in all 15 cases with a median 7219 (IQR 2432–17130) pg/mL.

Pathological changes in echocardiography were observed in 13/15 patients; the most common findings included valvular insufficiency: Mitral (9/15) and tricuspidal (8/15) and decreased left ventricular ejection fraction (6/15). In electrocardiography (ECG), various changes of ST-segment or T-wave (13/15), bradyarrhythmias (8/15), tachyarrhythmias (8/15), intraventricular conduction defects (12/15) were observed. Three patients out of all 15 had signs of myocarditis by elevated cardiac biomarkers in conjunction with clinical signs and ECG and echocardiographic findings, and one of them was diagnosed with myocarditis by cardiac MRI. Altered chest radiographs were found in 12/15 patients. Pleural effusion was found in nine patients by ultrasonography.

Link to SARS-CoV-2, all study patients were linked to SARS-CoV-2 by having been in contact with COVID-19-positive people 2–6 weeks before MIS-C symptoms developed. Only five patients out of the 15 were symptomatic during the acute COVID-19 phase, and three of them were tested for SARS-CoV-2 by PCR at that time – two were found to be positive. For the other 12 patients, SARS-CoV-2 RNA testing was completed at the time of MIS-C admission, and of this one patient had positive SARS-CoV-2 RNA by rapid molecular testing, but was negative by PCR. All 15 patients had a positive serology for SARS-CoV-2 [Table 2].

Treatment and clinical course seven patients of all 15 required admission to the pediatric intensive care unit (PICU) for a median two (IQR 1.27–2.73) days' stay because of hemodynamic instability, of whom five patients required inotropic support with epinephrine or norepinephrine. Oxygen support was required in six patients due to respiratory distress or desaturation, but mechanical ventilation was not needed.

Antimicrobials were prescribed for all the patients treated in the hospital. All received intravenous immunoglobulins (IVIG), glucocorticosteroids, and acetylsalicylic acid (AAS) according to the indications. Two children received methylprednisolone pulse therapy.

The median length of hospitalization was 15 (IQR 13–16.1) days for PICU patients and 19 (IQR 11.27–19.3) days for children treated on the hospital ward. There were no deaths among this group of patients.

DISCUSSION

This report describes our first clinical experience of Latvian patients with MIS-C. In our study, MIS-C cases occurred 2–6 weeks after acute illness or contact with a COVID-19-positive person after the COVID-19 infection peaked in Latvia. This was similar to the previous studies reported in Europe.[6] We observed a tendency for children to be hospitalized at a relatively late stage in their illness, as observed in Santiago. Moreover, in the case studies presented here, the children were most frequently treated in an outpatient setting with antibiotics used to treat other suspected diseases, including scarlet fever, gastrointestinal infections, or acute appendicitis. Neither the children's parents nor the outpatient doctors associated these conditions as a sequelae after the COVID-19, perhaps, due to the mild or even asymptomatic course of the disease in children. This is also the reason why diagnostic tests were performed less frequently following exposure to COVID-19, although symptoms were displayed after that. Since PCR and anti-SARS-CoV-2 antibodies can often

be negative, the careful acquisition of an epidemiological history is essential. To date, studies have indicated that males may be overrepresented.[7] In our study, 12/15 were boys and, overall, the majority of patients were previously healthy.

In our series, the median age was 8.8 years. Rafferty *et al.*, based on the available studies, reported that the median age of children who developed MIS-C varied from 7 to 10 years.[2] The most common clinical presentation was persistent fever along with dermatological, mucocutaneous and gastrointestinal features, similar to other reports.[8] Given that 100% of our study patients had acute gastrointestinal symptoms and all of them had multi-organ involvement, it has become essential to assess further the involvement of other organ systems in all children with a fever, and especially those with severe abdominal pain. For example, Belhadjer *et al.* reported gastrointestinal involvement in more than 80% of patients.[9] Gastrointestinal manifestations in MIS-C can present in a similar way to many other infectious diseases in children. In our study, abdominal pain was the most common gastrointestinal symptom. Two patients needed surgery because of this initial suspicion of acute abdominal symptoms. In the Jackson report, which described one clinical case, abdominal pain also mimicked acute appendicitis. In fact, all our patients had skin and mucocutaneous involvement. Dermatological manifestations are the top clinical manifestations in children with MIS-C, as mentioned in other studies.[10]

In the present study, we report that 100% of patients had cardiac involvement. The systematic review by Abrams *et al.* noted that 71% of MIS-C cases had cardiovascular symptoms.[11] These findings suggest that patients with MIS-C should always be closely monitored for cardiovascular function, since the majority of them have severe manifestations including shock, hypotension, arrhythmias, and myocarditis. Nevertheless, it is also important to monitor arterial blood pressure and other possible signs of shock requiring immediate treatment. Patients with multi-organ system involvement require medical care in a tertiary-level hospital from a multidisciplinary team.

Laboratory evidence of systemic inflammation, myocardial dysfunction, and coagulation activation has been consistently documented in the previous reports.[10] All children in the present study had positive initial laboratory criteria for strongly suspected MIS-C, such as elevated CRP and/or ESR plus lymphopenia or thrombocytopenia or hyponatremia. Given that they are easy to perform, these analyses are recommended as additional screening tools that can be used in an outpatient setting or a regional hospital.

There are known few clinical practice recommendations regarding treatment for MIS-C by several organizations.[5] Ramcharan *et al.* reported favorable outcomes in treatment plans with IVIG and corticosteroids.[10] Similarly, our experience showed good outcomes from using IVIG, corticosteroids, AAS, and anticoagulants.

Hospitalization was longer due to the general condition of the children. Seven patients of all 15 required admission to the PICU. Similar to our study, Tolunay *et al.* also reported median duration of hospitalization 12,5 days in an article "Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19: A case series experience in a Tertiary Care Hospital of Southern Turkey."[12]

Finally, this study has the limitation of representing a small case group. Only 15 children were enrolled. Collaboration is needed at national and international levels. Thus, a larger sample study should be used to confirm these results.

CONCLUSIONS

In the present pandemic, where the incidence of COVD-19 has peaked, every child with a fever should have a well-defined epidemiological history, and a careful clinical assessment of possible multiple organ-system involvement, with a special focus on those with severe abdominal pain and/or skin or mucocutaneous lesions. Before hospitalization or transfer to a university hospital, vital signs should be carefully monitored, intravenous rehydration and antibacterial therapy should be provided, and initial laboratory tests should be performed. Any signs of shock should be assessed and treated immediately. Both members of the public and medical staff need to be further educated about the possible late manifestations of COVID-19.

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