



CORONA VIRUS DISEASE-2019 AND ITS MYRIAD COMPLICATIONS IN CHILDREN: A CASE SERIES

Paediatrics

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) has caused significant morbidity and mortality worldwide. Children with COVID-19 can have varied clinical manifestations and presentations. **Case Presentation:** We present four children with COVID-19 and its complications with uncommon manifestations. Three children in this case series had unusual presentation of Multisystem Inflammatory Syndrome in children (MIS-C). In one child, MIS-C mimicked acute appendicitis for which he was operated upon. Second child presented with acute pancreatitis and third child had MIS-C with intravascular hemolysis. One child in our series had unusual manifestation of COVID-19 i.e croup. **Conclusion:** COVID-19 in children may have a myriad of complications with unusual presentation and manifestations. One should always look for these. Early diagnosis and management in some of these complications is imperative for better outcome.

KEYWORDS

Coronavirus; Multisystem Inflammatory Syndrome in Children; Croup; Pancreatitis; Appendicitis; Hemolysis; Optic Neuritis.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) has wreaked havoc with significant morbidity and mortality worldwide. It is generally milder in children but they still can have varied clinical manifestations and presentations¹. Fever and cough are the most common clinical features of COVID-19 in children but atypical presentations such as anosmia, croup, myocarditis, encephalopathy, stroke, Guillain-Barre Syndrome and various cutaneous manifestations may occur. Children are also prone for post-infectious complications, notably, Multisystem Inflammatory Syndrome in children (MIS-C) and long COVID syndrome^{1,2}. Some of the manifestations are also linked to the Corona virus variant. Pediatric croup has more often been found to be associated with omicron variant³. Studies published till date have shown, respiratory system to be the commonest system involved but literature is still evolving with documentation of new manifestations. We present four children with COVID-19 and its complications with uncommon manifestations.

Case Presentation

Case 1

Nine-year-old male child presented with pain abdomen, high grade fever and vomiting for one day. Pain was severe and confined to right lower abdomen. Fever was intermittent, maximum documented up to 104⁰ Fahrenheit. After initial evaluation, with clinical impression of acute appendicitis, he was admitted in surgery department of our institute and was operated for that. On day five post operation, the child was shifted to our department in view of persistent high grade fever, appearance of generalized maculo-papular rash and loose stools.

On examination, he was sick, irritable, had heart rate 190/min with feeble peripheral pulses, respiratory rate 40/min and blood pressure 82/40 mmHg. He had generalized maculo-papular erythematous rash. Possibility of sepsis with shock was kept and he was initiated on oxygen therapy, fluid boluses, inotropes (adrenaline @ 0.2 microgram/kg/min) and intravenous (i.v.) antibiotics (vancomycin @ 20 mg/kg 8 hourly and meropenem @ 20 mg/kg 8 hourly).

On investigation (Table 1), his blood culture and urine culture were sterile. There was history of Covid-19 contact one month back. As child also had rash, abdominal symptoms, possibility of MIS-C was thought of. His severe acute respiratory syndrome corona virus-2

(SARS COV-2) antibodies were positive. He had lymphopenia, thrombocytopenia, elevated inflammatory parameters, increased serum lactate dehydrogenase (LDH) and pro brain natriuretic peptide (pro-BNP), transaminitis, hyperferritinemia. Thus, diagnosis of MIS-C was considered, as investigations were more in favour of it and patient was started on intravenous immunoglobulin (IVIG) (2 gm/kg over 18 hours) and i.v. methylprednisolone (2 mg/kg/day) was given for five days followed by oral prednisolone (2 mg/kg/day). The child improved within 24 hours of this treatment. Gradually, inotropes were tapered and antibiotics were stopped after five days. His echocardiogram was normal. Histopathological examination of appendix did not show any sign of inflammation. He was discharged on aspirin and tapering doses of oral prednisolone for four weeks. He is doing fine on follow-up.

Case 2

A 12-year-old girl was admitted with fever for two days, pain abdomen and vomiting for one day. Pain abdomen was localised to epigastrium, was severe, colicky and getting relieved on bending forward. She also had 6-7 episodes of vomiting in last 24 hours. On examination, she was afebrile. Her pulse rate was 86/minute, respiratory rate 22/ minute and blood pressure 102/70 mm Hg. Abdominal examination revealed mild tenderness in epigastrium and left hypochondrium. Rest of the systemic examination was unremarkable. Investigations showed markedly elevated serum amylase (1448 IU/L) and lipase (605 IU/L) and ultrasound abdomen was suggestive of acute focal pancreatitis. The child was kept nil per-oral and initiated on i.v. fluids, ondansetron and pantoprazole. On day two of admission, the child developed shock and respiratory failure. She required inotropes, i.v. antimicrobials and mechanical ventilation. Laboratory investigations (Table 1) revealed neutrophilic leucocytosis with lymphopenia, thrombocytopenia, elevated inflammatory parameters, increased LDH and pro-BNP, transaminitis and elevated SARS Cov-2 antibodies. Contrast enhanced computed tomography (CECT) abdomen showed normal pancreas. Two-dimensional Echocardiography showed cardiac dysfunction with ejection fraction of 30-35%. Clinical possibility of MIS-C was considered.

She was initiated on i.v. methylprednisolone (30 mg/kg/day) and IVIG (2 gm/kg over 12 hours). The child remained on mechanical ventilation and inotropes for three days and was gradually weaned off. After five

days of methylprednisolone, oral prednisolone @2 mg/kg/day was started. She remained hospitalized for 12 days and was discharged on tapering doses of prednisolone, aspirin (5 mg/kg/day). The child is now under follow-up and doing well.

Case 3

Three-year-old girl presented with vomiting, loose stools and fever for two days. She also had lethargy, passage of cola-coloured urine, sudden onset of paleness of body and yellowish discoloration of eyes for one day. On examination, she was irritable, had heart rate of 160/min with feeble peripheral pulses and respiratory rate 46/min. She had severe pallor, icterus, bilateral basal crepitations on chest auscultation and hepatomegaly (liver span 11 cm).

Possibility of acute gastroenteritis with no dehydration with intravascular hemolysis (IVH) with severe anaemia with congestive cardiac failure (CCF) was kept. She was initiated on maintenance fluids, urine alkalinisation and 1 unit of packed red blood cells was transfused.

The child continued to have high grade fever and irritability after three days of admission. Laboratory investigations (Table 1) showed hemoglobin 5 gm/dl, neutrophilic leucocytosis, hemoglobinuria, unconjugated hyperbilirubinemia, elevated inflammatory parameters, increased serum LDH and pro-BNP, transaminitis, markedly elevated serum ferritin (> 2000 ng/ml) and presence of SARS Cov-2 antibodies. Her direct antiglobin test (DAT) was negative. Cerebrospinal fluid (CSF) examination and echocardiography was normal. Thus, possibility of MIS-C with IVH was kept. She was given IVIG (2 gm/kg over 16 hours) and i.v. methylprednisolone (2 mg/kg/day) for five days. The child responded to treatment. She was discharged on aspirin (5 mg/kg/day) and tapering doses of oral prednisolone, oral iron, folic acid and multivitamins and kept on follow-up.

Case 4

Six-month-old male infant presented with low grade fever, cough and stridor for one day. His mother had COVID-19 disease two weeks back. On examination, he was active and playful. His vitals were stable with SpO₂ 97% on room air. He had inspiratory stridor. On investigations, (Table 1) his blood counts were normal, Reverse-transcriptase polymerase chain reaction (RT-PCR) for SARS CoV-2 was positive. His multiplex PCR for influenza A and influenza B viruses was negative. Possibility of croup secondary to Covid-19 infection was kept. He was initiated on nebulization with adrenaline and injection dexamethasone (0.15 mg/kg) was given stat. He improved in next 24 hours and discharged for home isolation.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

DISCUSSION

Covid-19 has varied clinical manifestations and complications in children. MIS-C is one of life threatening complications of this viral infection¹. Three of our cases had unusual presentation of MIS-C. Two children presented with acute abdomen. First case presented with clinical features suggestive of acute appendicitis, although, histopathological examination did not show inflammation in appendix. Other child had presentation of MIS-C with pancreatitis. Her initial clinical features and investigations were suggestive of the same. Her CT scan of abdomen, which was done after 72 hours of symptoms onset, showed normal pancreas. Patients with mild pancreatitis may have normal imaging as seen in the index case but is not a feature of acute severe pancreatitis⁴⁵. So, multiorgan dysfunction in this child was secondary to MIS-C and he also responded to the treatment for the same.

Abdominal symptoms like pain abdomen, vomiting are the most common manifestations of MIS-C after fever^{6,7}. A systematic review by Rouva et al, on acute abdomen in MIS-C showed that 60.5% of children with MIS-C had gastrointestinal (GI) symptoms. Nearly one third of these with GI symptoms mimicked acute abdomen and half of them underwent laparotomy. However, one fourth of these children with features of acute abdomen were found to have true surgical pathologies like appendicitis, peritonitis, ileus⁷. MIS-C can mimic acute appendicitis and acute pancreatitis and also these can be one of the manifestations of MIS-C^{7,9}. Treating pediatric surgeon should be aware of MIS-C as a mimicker of acute abdomen as these patients require non-surgical management including immunosuppressive/anti-inflammatory therapy. Moreover, pediatrician should also be aware of

possibility of MIS-C in children with co-existence of true surgical emergencies, as, delay could prove to be catastrophic.

Third child presented with IVH. IVH has been reported earlier in COVID-19 patients as a consequence of complement activation¹⁰ but direct antiglobin test for warm and cold antibodies in index child was negative. Etiopathogenesis of IVH in COVID-19 is still not clear. Complement mediated hemolysis is one of the proposed mechanisms, but there are various case reports of coombs negative IVH in these patients. One hypothesis is viral tropism for erythrocytes, which further needs research^{11,12}. Thrombotic microangiopathy (TMA)/ hemolytic uremic syndrome spectrum disorders have been reported in COVID-19 and MIS-C patients and may have similar clinical presentation as seen in the index case¹³. But, this child had normal renal functions, normal platelet counts (Table 1) and patient's peripheral smear did not show schistocytes. She responded to i.v. methylprednisolone followed by tapering dosages of prednisolone. IVIG and methylprednisolone have been shown to be standard of care in children with MIS-C in various treatment protocols^{6,14}. Intravenous methylprednisolone has been used in dosages of 2-30 mg/kg/day in MIS-C. Children with MIS-C and severe disease would require high dose i.v. methylprednisolone therapy (10-30 mg/kg/day) for 3-5 days¹⁴.

Fourth child in this series had uncommon manifestations of COVID-19. He had croup as a presentation, which has been reported earlier but is not a common feature of COVID-19¹⁵. His multiplex PCR for Influenza A and Influenza B viruses was negative. Although, we could not rule out all the possible viral etiologies for croup and coinfection with another virus, temporal association suggests it to be secondary to COVID-19. The management of croup associated with COVID-19 is essentially similar as for other viral etiologies. Index child responded to single dose dexamethasone and nebulization with adrenaline.

To conclude, COVID-19 in children may have a myriad of complications with unusual presentation and manifestations. MIS-C can mimic or present with acute abdomen like acute appendicitis or acute pancreatitis. One should always look for these. Early diagnosis and management in some of these complications is imperative for better outcome.

Table 1: Laboratory Investigations of the Patients

Investigations	Case 1	Case 2	Case 3	Case 4
Hemoglobin (g/L)	109	84	5	109
WBC (103/L)	4.9	13.6	13.4	8.5
(Differential count)	N76% L20%M3 (%)	(N88% L7% M4%E1%)	(N81% L14% M4%E1%)	(N52% L43%M4 %E1%)
Platelet count (103/L)	79	100	161	225
ESR (mm at 1hr)	50	19	15	16
C-Reactive Protein (mg/L)	18	24	22.5	<6
Blood Urea (mg/dL)	24	17	19	13
Creatinine (mg/dL)	0.8	0.4	0.4	0.23
Serum Bilirubin (mg/dL)	0.4	0.32	9.9 (Indirect- 9.1)	
AST (U/L)	62	91	128	
ALT (U/L)	45	50	27	
Serum Ferritin (ng/ml)	1500	214	>2000	
Troponin I (pg/ml)	0.04	267	3.1	
NT-pro BNP (pg/ml)	8161	>35000		
Serum Triglycerides (mg/dl)	143	618		
D-Dimer (<0.4 mcg/ml)	3.408	11.17	13.82	
Serum LDH (U/L)	900	777	1511	
Procalcitonin (ng/ml)	100	24.39		
SARS-CoV-2 antibody IgG (units)	195	17.6	212.2412	
Urine examination.	Normal.	Normal.	Hazy, RBC 8-10/ HPF, Hb +	
RT-PCR Covid -19.	Negative	Negative	Negative	Positive

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate, Hb, hemoglobin; LDH, lactate dehydrogenase; MOG, Myelin oligodendrocyte glycoprotein; NMO; neuromyelitis optica; NT-pro BNP, N-terminal pro b-type natriuretic

peptide; RBC, red blood corpuscles; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome corona virus-2; WBC, white blood corpuscles.

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