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RESEARCH ARTICLE

A CASE REPORT ON MULTISYSTEMIC INFLAMMATORY SYNDROME- CHILDREN; HOW THE DIAGNOSIS AND TREATMENT COULD BE CHALLENGING

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Abstract

Although COVID 19 infections in children are generally mild and non-fatal, there is increasing recognition of a multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, leading to severe illness and long-term sequelae. Even though there is some evidence that the MIS-C is a post-viral immunological reaction to COVID-19, understanding of the immune response induced by SARS-CoV-2 remains unclear.Various local and international guidelines are being widely practiced in the diagnosis and management of patients with MIS-C. A case report of a young child who was diagnosed and managed as MIS-C is discussed here. The diagnostic challenges with the available case definitions and currently accepted treatment options are elaborated herein.

Introduction:-

Case History

A two-year and three-month-old boy was admitted to the teaching hospital, Karapitiya, with a history of fever for two days. The fever was of high grade and intermittent. The child was well in between fever episodes. Systemic inquiry did not reveal symptoms related to respiratory, cardiovascular, abdominal, urological, or neurological systems. He had been infected with COVID 19 one month ago with mild upper respiratory tract symptoms, with an uncomplicated recovery. There were no chronic illnesses in the past. The child's immunization and development history were age-appropriate.

On general examination, the child was irritable and crying. Body temperature was 102^0F. There was no pallor, cyanosis, or icterus. There was no conjunctivitis. Enlarged multiple tender cervical lymph nodes (1.5X2 cm) were noted bilaterally, which were firm in consistency. Hydration was adequate. Skin rashes were not observed. His weight and height were 12 kg and 93cm which were between the 10th and 25th and on the 90th centile respectively.

His pulse rate was 120 bpm which was regular and of good volume. Blood pressure was 89/59 mmHg. Systolic blood pressure was in the 50th centile, and diastolic blood pressure was in between 50th and 90th centile. Capillary refill time was less than two seconds. Dual rhythm was noted on auscultation with no audible murmurs.

He was not dyspneic, and his respiratory rate was 30 breaths per minute. Oxygen saturation was 100% on room air. Auscultation of the lungs was normal. The abdomen was soft and non-tender. There was no hepatosplenomegaly.

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External genitalia examination was normal. Bilateral pupils were equal in size. There was no neck stiffness. The child was able to walk. The throat and ear examinations were normal.

COVID 19 antigen test was negative. Initial blood investigations revealed neutrophil leukocytosis with normal hemoglobin and platelet level, elevated C-reactive protein of 60 mg/dl, and Erythrocyte Sedimentation Rate of 11 mm in 1st hour. Liver functions showed raised AST with normal ALT. ALP was also elevated. Blood urea and electrolytes were within the normal range. Serum sodium was 133 mmol/l, and potassium was 4.5 mmol/l. The urine full report was normal. Blood and urine cultures were sent. Input-output was measured. The child was put on paracetamol 15mg/kg for 6-hourly.

On the 3rd day of illness, the child was having high-temperature spikes of 103^0F. He was less active and had reduced oral intake. There had been one episode of vomiting and three episodes of diarrhea. The urine output was maintained >1ml/kg/hour. Hisvital parameters were continuously monitored and were within the normal range. Investigations revealed mild hyponatremia, normal troponin I level, normal triglyceride level, and elevated serum Lactate Dehydrogenase level. He was started on intravenous cefotaxime 50 mg/kg 8 hourly.

On the fourth day of illness, the fever continued. Vomiting and diarrhea were settled. Feeding and urine output was adequate. Nevertheless, the child was lethargic and irritable. Vital parameters were within the normal range. There were no abnormalities detected in respiratory, cardiac, or neurological examination. Mild hyponatremia of 133 mmol/l was noted. Blood sugar was within the normal range. Blood culture and urine culture were negative. It was decided to change the antibiotic to intravenous meropenem 440mg 8hourly.

On the fifth day, fever spikes continued, and the child was very irritable and ill-looking. There were four episodes of non-mucoid diarrhea. He was put on intravenous fluid at full maintenance. The patient was catheterized, and urine output was measured hourly. Urine output was >1ml/kg/hour. He had tachycardia, and blood pressure was maintained at 50th centile. 2D echo revealed normal biventricular functions, and the coronary artery sizes were within the normal limit. Ultrasound abdomen had been done, which revealed dilated large bowel loops suggestive of colitis. There was no evidence of appendicitis, pyelonephritis, or ascites. A lumbar puncture was done to exclude meningitis and was negative. Chest X-ray was normal. Plasma D- dimers were elevated. Serum ferritin and fibrinogen were at the normal upper limit.

Meanwhile, antibodies for COVID 19 infection came as positive. It was decided to start treatment as a case of MIS-C. Intravenous methylprednisolone 2mg/kg infusion and intravenous immunoglobulin 2g/kg were administered as a slow infusion. Aspirin was started at a dose of 5mg/kg. On the same day the evening, his blood pressure was 70/30 mmHg which was below the 50th centile. Even after 10ml/kg fluid bolus blood pressure did not improve. Thus, it was decided to start on intravenous dopamine 10 µg/kg/min infusion.

The next day fever subsided, and the child's general condition improved. He was able to tolerate oral feeds better than the previous day. Thus, intravenous fluid was gradually tailed off. Dopamine infusion was also gradually tailed off. He was able to maintain a satisfactory urine output. Intravenous methylprednisolone 2mg/kg was given. Intravenous antibiotics were continued.

On the seventh day of illness, the child was afebrile active and able to tolerate oral feeds. Vital parameters and urine output was maintained satisfactorily. Intravenous methylprednisolone third pulse was given.

On the eighth and ninth days, the child was active, and hemodynamics were stable. Repeated blood investigations revealed marked improvement of inflammatory markers. The child was discharged from the ward with the advice to continue 50mg of aspirin nocte up to fourteen days with a follow-up at the general pediatric clinic in one week.

Table 01:- Investigation profile.

	Day 02	Day 04	Day 05	Day 09
FBC				
WBC 10^3/µl	11	18		16
N %	72	79		27
L%	20	17		62
Hb g/dl	12	11		11

PLT 10^3/µl	324	298		722
CRP mg/l	60	162	203	28
ESR in 1st hour	11			
Sodium mmol/l	133	130	133	138
Potassium mmol/l	4.5	5.1	3.7	4.9
Plasma D-dimer mg/L FEU			0.69 (<0.5)	
AST U/L	57	23		33
ALT U/L	38	19		22
ALP U/L	286			3
Total protein g/l	62			
Albumin g/l	41			
Total bilirubin µmol/l	14	4		
Urea mg/dl	31	28		36
Creatinine µmol/l	23	22		
Urine full report Pus cells Red cells	 Occasional Nil			
Blood culture	No growth			
Triglyceride mg/dl	139			
Lactate dehydrogenase	265			
HS Trop I ng/l	14.3 (<19)			
Fibrinogen			4.1g/l	
CSF full report Protein mg/dl Glucose mg/dl Polymorph/mm^3 Lymphocyte /mm^3			 15 71 00 00	
CSF culture			No growth	
2 D Echo			No dilated coronaries Normal EF	
COVID 19 RAT	negative			
COVID19 antibodies			Positive	
EBV antibody			negative	

Discussion:-

COVID 19 infection has recently been identified as associated with a novel set of clinical manifestations presently called multisystem inflammatory syndrome in children (MIS-C). While the incidence of MIS-C is uncertain, it appears to be a relatively rare complication of COVID-19 in children and adolescents, occurring in less than 1 percent of children with confirmed SARS-CoV-2 infection. Most MIS-C cases have occurred in older children and adolescents who were previously healthy. The affected age ranges from 1 to 20 years.

The exact pathophysiology of MIS-C is yet to be understood. It has been suggested that dysregulated host immune response to the virus results in this syndrome. A massive surge of cytokine induces an undue inflammatory response causing multiorgan failure. Even though there are clinical similarities with Kawasaki disease and macrophage activating syndrome, MIS-C appears to have a distinct immunophenotype. In research, it has been found the similarities between the adult hyperinflammatory response for COVID 19 infection and MIS-C, suggesting antibodies might play a role in both conditions.

The average duration between acute COVID-19 infection and onset of MIS-C symptoms is two to six weeks. There are reported cases of MIS-C during the active COVID 19 infection too. Our patient had got the illness in the post-COVID sixth week. Commonly reported complaints are fever, gastrointestinal symptoms such as abdominal pain, vomiting, diarrhea, rash, conjunctivitis, mucus membrane involvement like red or swollen lips and strawberry

tongue, neurocognitive symptoms like headache, lethargy, and confusion. Persistent fever that lasts more than three to five days is characteristic of MIS-C. This can vary from mild to high grade. In addition, respiratory symptoms, sore throat, myalgia, swollen hands/feet, and lymphadenopathy can present less commonly. Although features of MIS-C overlap with those of Kawasaki disease, studies have found a broader spectrum of MIS-C symptoms. In addition to a broader clinical spectrum, there are several other distinct features of MIS-C compared with Kawasaki disease, including the age and ethnicity, and show more significant elevation of inflammatory markers.

Common laboratory abnormalities noted include the following. Lymphocytopenia with neutrophilia, mild anemia, and thrombocytopenia will be seen in the complete blood count. Elevated inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), d- dimers, fibrinogen, ferritin, procalcitonin, and interleukin-6. Elevated CRP had been noted in 90-100 % of reported cases. It is distinguished that these inflammatory markers appear to correlate with the disease severity.

Elevated cardiac markers are troponin and BNP or N-terminal pro-BNP (NT-pro-BNP). In addition, hypoalbuminemia, mildly elevated liver enzymes, elevated lactate dehydrogenase, hypertriglyceridemia could be noted.

Echocardiographic findings may include depressed LV function, coronary artery abnormalities, including dilation or aneurysm, mitral regurgitation, or pericardial effusion.

According to the WHO guideline, there has to be a persistent fever for more than three days. There should be at least two of the following;

1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet).
2. Hypotension or shock.
3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),
4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).

Along with these features, elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin should be present. Moreover, there should be no other apparent microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. Evidence of COVID-19 (RT-PCR, antigen test, or serology positive) or likely contact with patients with COVID-19 should be present.

Our patient presented on the 2nd day with a persistent high-grade fever. He had tender cervical lymphadenopathy and later developed vomiting and nonmucoid diarrhea due to colitis, as suggested by the ultrasonography. He became lethargic and drowsy. He had absolute lymphopenia with neutrophilia and mild anemia in the complete blood count. He also had mild hyponatremia. CRP was gradually increased from 60mg/l on the second day to 203 mg/l on the fifth day of the disease. His COVID 19 serology was positive. Even though the echocardiogram did not reveal any abnormality, he developed hypotension on day five. Blood and urine cultures were negative, CSF was non suggestive of infectious focus, and his chest X-ray was normal. Abdominal ultrasonography did not reveal signs of appendicitis. Thus, it was considered that clinical findings and investigation results are unlikely to be due to sepsis. Our patient fulfilled some of the criteria of WHO definition for severe MIS-C even though the initial presentation was not highly indicative of it. He responded well to steroid and intravenous immunoglobulin, which were administered according to the Sri Lanka College of Pediatricians guideline for MIS-C management.

The Center for Disease Control and Prevention of United States (CDC) case definition for MIS-C is a fever for more than 24 hours, with laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalization, with multisystem organ involvement. Similarly, there should not be any plausible alternative diagnoses. Positive COVID 19 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-case within the four weeks before the onset of symptoms should be present. This might be a valuable tool if the patient presents in the early course of disease like in our patient. According to the Royal College of Pediatrics and Child Health definition of MIS-C, even single system involvement is accepted as the main feature.

However, as our patient did not show all the typical clinical features and positive results of MIS-C laboratory markers, diagnosis of the MIS-C was somewhat delayed. This implies that more sophisticated and sensitive gears should evolve to diagnose this life-threatening condition associated with COVID 19 infection early.

A multidisciplinary team approach should be taken if MIS-C is suspected or diagnosed, including pediatric intensivist, cardiologist, immunologist, and rheumatologist. Because many cases met the diagnostic criteria of classic or incomplete Kawasaki disease, most reported MIS-C cases are being treated with intravenous immunoglobulin with or without aspirin. In high-income countries, patients with severe MIS-C receive immunomodulatory agents such as infliximab, tocilizumab, and anakinra. Steroids such as methylprednisolone, dexamethasone, or prednisolone have become extensively used for MIS-C. Thus, prospective clinical trials are needed to identify the role of steroids, the optimal dose, and the appropriate agent. hypotension in children with MIS-C is often fluid-resistant, and vasopressors would be added if necessary. Epinephrine is endorsed as the first-line treatment for children, and norepinephrine is added if the shock persists. Dobutamine has also been proposed in patients with severe myocardial dysfunction because of its selective inotropic effect. The initiation of broad-spectrum antibiotics is also appropriate because the clinical presentation makes it difficult to exclude bacterial infection.

Nevertheless, antibiotic treatment should be stopped once the infection has been excluded and the patient is improving. Coronary artery aneurysms have been reported in children with severe MIS-C and those with Kawasaki-like disease and children showing only fever and inflammation. Therefore, cardiac assessment and follow-up are essential in all cases. All patients need echocardiographic assessment on presentation and frequent electrocardiogram monitoring in severe cases. If coronary artery injury has occurred, follow-up echocardiograms are needed at discharge from the hospital and after 2–6 weeks. MIS-C has elevated D-dimers, which, in some guidelines, is used as a guide for giving anticoagulants.

When the inflammatory laboratory markers have normalized, children can be discharged from the hospital; once they are afebrile, normotensive, and well hydrated. Close follow-up is very imperative because the natural history of MIS-C is still blurred.

Summary

Multisystemic inflammatory syndrome in children (MIS-C) associated with COVID-19 can lead to serious life-threatening complications and long-term sequelae. The clinical and laboratory features of MIS-C can be overlapping with those of Kawasaki disease and toxic shock syndrome. Hence MIS-C is a condition which needs to be diagnosed by a team with expertise in identifying the specific clinical and laboratory features and by excluding the other possible differential diagnoses. Pathophysiology of MIS-C is still unclear, and possible mechanisms include an antibody or immune dysregulation due to cytokine storm. Most cases of MIS-C were managed following the standard protocols for Kawasaki disease, which include intravenous immunoglobulin, steroids, and aspirin. Inotropic or vasoactive agents are required in patients with cardiac dysfunction and hypotension. Anticoagulation is also used if there is a hematological indication. Further research and clinical evidence are required for a better understanding of the pathophysiology of this disease and to change the standard management protocols.

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