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REVIEW ARTICLE

Multisystem Inflammatory Syndrome in Children (MIS-C) of Asian Countries: A Mini-Literature Review on its Clinical Characteristics and Outcomes

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ABSTRACT

COVID-19 pandemic though has reached endemic levels in most of the countries, it has left an indelible mark on the healthcare systems across the world. One of the emerging challenges faced by physicians and researchers all around the world is the increased incidence of Multisystem inflammatory syndrome in children (MIS-C). Most of the research work conducted till date focusses on the pathophysiology, management and treatment of this syndrome. Multisystem inflammatory syndrome in children has been found to be a consequence of hyperactive immune system resulting from cytokine activation and release of immune complexes subsequent to COVID-19 infection. This condition is also associated with multisystem dysfunction which if not diagnosed early and not treated promptly, could result in an increased mortality among children. Most of the cases have been reported from European and American countries, but not many from Asia.

This literature review provides for plausible reasons as to why the incidence of multisystem inflammatory syndrome in children has been less in Asian countries compared to the rest of the world. It also gives insights into the treatment protocols for multisystem inflammatory syndrome in children followed by hospitals in these countries and also highlights how different MIS-C is from Kawasaki disease in terms of clinical presentation since both these conditions share a common disease spectrum. This review also lists out the clinical features and treatment followed in such patients belonging to Asian countries.

Keywords: Multisystem inflammatory syndrome, children, COVID-19, Kawasaki disease, Asian countries

Introduction:

COVID-19 has emerged as a disease of immense concern in the entire world. It has indeed opened a Pandora's box upon which we stand with much consternation. According to the World Health Organization (WHO) statistics, the total confirmed cases of COVID-19 in the world as on 21st March 2023 stand at 76,10,71,826 cases[1]; amongst which 4,46,96,984 confirmed cases have been reported from India itself.[2] Deaths reported in the world till date are 68,79,677,[1] while 5,30,308 deaths have been recorded in India.[2]

One of the post-COVID complications noticed in children, albeit in less numbers worldwide, that has caught the attention of doctors and researchers alike is the emergence of multisystem inflammatory syndrome (MIS) 4-6 weeks after COVID infection.[3] Since it resembles Kawasaki disease (KD) in its clinical presentation, such affected children were treated with standard protocol for KD which included intravenous immunoglobulin, pulse dose steroids, inotropic agents, low dose aspirin, etc.[4] The first case of multisystem inflammatory syndrome in children [MIS-C] was reported in April 2020 in the United Kingdom, following which more such cases were observed in United States, Canada, Europe and South Africa. Surprisingly, very few numbers were reported from China and other Asian countries when these countries had the highest numbers of actual cases of COVID-19.

A lag of several weeks has been observed between the peak of COVID-19 cases and that of rise in MIS-C cases. In London, the peak of COVID-19 cases occurred in the first two weeks of April, while the spike of MIS-C cases occurred in the first two weeks of May. This month-long gap coincided with the development of acquired immunity, thus, indicating that MIS-C represents a complication of the virus post-infection rather than acute infection.[5]

Case definition: With a rise in MIS-C cases, the Council of State and Territorial Epidemiologists [CSTE] and Centre for Disease Control and Prevention [CDC] have developed a new case definition which is to be used for onset of MIS-C type illness after 1st January 2023. According to the new case definition, MIS-C is ascertained if age of the affected child is less than 21 years with documented fever of >38°C; requiring hospitalization or results in death of the child; C-reactive protein levels >3mg/dL; with cardiac (left ventricular ejection fraction <55%, dilatation of coronary arteries/aneurysm formation, elevated troponin levels), muco-cutaneous (rash, oral mucosal inflammation, conjunctivitis, erythema/edema of hands and feet), hematological (thrombocytopenia, lymphocytopenia) and/or gastric involvement (abdominal pain, nausea, vomiting, diarrhea); presenting with shock; has met laboratory criteria for SARS-CoV2 infection in the past 2 months (detection of SARS-CoV-2 RNA and/or detection of SARS-CoV-2 specific antigen in clinical specimens, detection of SARS-CoV-2 specific antibodies in plasma, serum or whole blood during current illness or during hospitalization); and presence of a close contact who has suffered from COVID-19 infection within 2 months of the child requiring hospitalization.[6]

Since very few studies exist that report the incidence of MIS-C in Asian countries, we have attempted to conduct a literature review to provide for recent evidence with respect to MIS-C infection in terms of less number of cases reported from Asian countries (even though incidence and prevalence of typical Kawasaki disease is more common in Asian countries); its pathophysiology, outcome and treatment protocols followed in these countries. It also highlights how different MIS-C is from Kawasaki disease in terms of clinical presentation since both these conditions share a common disease spectrum.

Methodology:

A systematic search of PUBMED database was done using keywords 'multisystem inflammatory syndrome in children', 'Asia' and included articles (review articles, meta-analysis, systematic reviews, case reports, case series, clinical studies, randomized control trials) between March 2020 to March 2023. Articles published in English language were included in this study. A total of 28 records were obtained; 20 records were included in this study (Figure 1) with a total sample size of 423 patients with MIS-C between the age group of 1-14 years. 16 patients died during the course of treatment as they suffered from severe type of MIS-C; case fatality rate being 3.7%. The clinical characteristics of patients included in this study are given in Table 1.

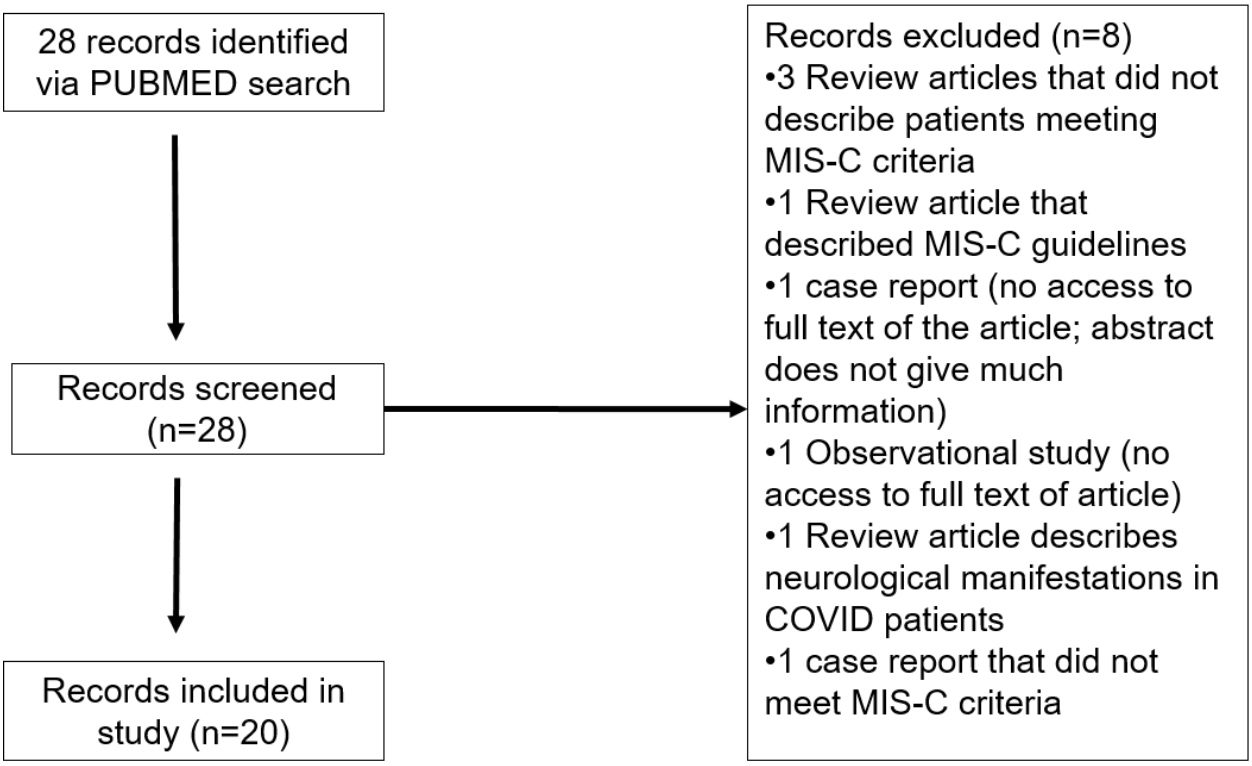

Figure 1: Description of study selection

Clinical spectrum:

Fever was observed in 420 patients. The other common symptoms being abdominal pain, conjunctivitis, rash all over the body, nausea, vomiting and diarrhea. 106 children were in shock and 16 patients succumbed to the disease. Almost all patients received IVIG, steroids and antibiotics as first line of treatment; 8 patients requiring dialysis to improve renal function. Mechanical ventilation, non-invasive ventilation, high flow nasal cannula were used in critically ill patients. Almost all patients had elevated inflammatory markers especially C-reactive protein, procalcitonin and ferritin levels. Laboratory results revealed lymphocytopenia, leukocytosis, anemia in majority of cases. 2-D echocardiography showed decreased ejection fraction, left ventricular systolic dysfunction, coronary artery dilatation in most of the patients.

Nassif et al reported a case of MIS from Lebanon. This patient showed predominantly cardiac symptoms including cardiogenic shock. Other constitutional symptoms like fever, myalgia and headache were also present. It was only on day 3 of admission that prompted for a change in treatment when a positive serology for COVID-19 was received. This case also drives the fact that prompt diagnosis can decrease the mortality rates among children suffering from MIS.[22]

Nadua et al reported incidence of MIS-C in 12 children in Singapore during the peak of Delta wave in 2021. Prior to this, no such cases were reported as the number of children infected with COVID-19 was very low. But during the Delta wave period (year 2021), nearly 20,000+ children were infected with COVID-19; this also increased the incidence of MIS-C in such children.[24]

Gurlevik et al studied the occurrence of neurological manifestations in MIS-C patients in Turkey which included encephalopathy, cognitive changes (visual, auditory or tactile hallucinations), meningeal irritation and presence of multiple micro hemorrhages in MRI brain suggestive of vasculitis and stenosis of middle cerebral artery. Cerebrospinal fluid analysis in such patients was suggestive of non-infectious inflammatory processes. The study concluded that neurological manifestations of MIS-C patients could be the result of immune mediated responses. Vascular endothelial damage triggered by an exaggerated cytokine release could be responsible for damage of blood brain barrier.[27]

Table 1: Clinical characteristics of Multisystem inflammatory syndrome in pediatric patients included from Asian countries

PMID	Article type	First Author	Number (Male; Female)	Age (years)	Clinical presentation	Shock	Medications	Respiratory support	2D ECHO findings	Renal support	Lab markers	Death
34221480	Case series	Al Maskari N[7]	6 (4;2)	1-11 years	Fever; Abdominal pain (n=4); Diarrhea (n=2); Conjunctivitis (n=4); Edema (n=4); Lymphadenopathy (n=4); Hepatosplenomegaly (n=2)	n=3	IVIG; Steroids; Inotropic support (n=2); Tocilizumab (n=1); Antibiotics; Aspirin (n=5); Anticoagulants (n=5)	Ventilation (n=1)	Depressed left ventricular function (n=1); Mild pericardial effusion (n=1)	Nil	Elevated inflammatory markers	0
34259880	Observational study	Patnaik S[8]	21 (13; 8)	8.48±4.3 years	Fever (n=18); Rash (n=17); Conjunctivitis (n=12); Diarrhea (n=16); Vomiting (n=8); Abdominal pain (n=10); Cough (n=5); Respiratory distress (n=12)	n=9	IVIG (n=7); Steroids (n=20); LMWH (n=20); Inotropes (n=9)	Mechanical ventilation, NIV & intubation (n=5)	Low EF (n=10)	Nil	Elevated inflammatory markers	0
36137147	Observational study	Rostami-Maskopaee F[9]	167 (96; 71)	2-8 years	Fever (n=167); Cardiac symptoms (n=89); Renal symptoms (n=59); Respiratory (n=89); Hematological (n=142); GIT (n=147); Skin (n=85); Neurologic (n=48); Conjunctival injection (n=42); Cervical lymphadenopathy (n=8); Strawberry tongue (n=1)	n=46	IVIG (n=154); Steroids (n=138); Steroids + IVIG (n=125); Antiplatelet (n=105); Anticoagulation (n=96); Antibiotics (n=73); Vasoactive medication (n=74); Immune modulators (n=7)	Low flow nasal cannula (n=69); Intubation (n=20); MV (n=19); High flow nasal cannula (n=13); NIV (n=5)	Low EF (n=30); Pericardial effusion (n=40); CAA (n=1)	Dialysis (n=2)	Positive RT-PCR (n=35); Exposure to COVID-19 (n=126); Leukopenia; Elevated ESR, Troponin, D-dimer;	10

35831257	Clinical notes/Case report	Fukuzawa S[10]	1 (1;0)	8 years	Fever; Right cervical lymphadenopathy; Bilateral conjunctival injection; inflammed lips; abdominal pain; vomiting; diarrhea	n=0	IVIG; Steroids; Aspirin;	Nil	EF = 75.1%; Pericardial effusion	Nil	Negative RT-PCR; Positive Serology; CRP increased	0
33904379	Case report	Fukuda S[11]	1 (1;0)	9 years	Fever; Erythema in groin & pubic areas; conjunctivitis, strawberry tongue, diarrhea	n=0	IVIG	Nil	Normal	Nil	Positive RT-PCR; Lymphocytopenia; CRP increased; Raised NT pro-BNP, Troponin-T, Pro-calcitonin	0
34087834	Case series	Asseri AA[12]	5 (2; 3)	2 to 11 years	Fever (n=5); Diarrhea (n=4); Abdominal pain (n=5); Rash (n=3); Conjunctivitis (n=3); Lymphadenopathy (n=3); Respiratory failure (n=3)	n=1	Vasopressors (n=4); IVIG (n=5); Aspirin (n=3); Steroids (n=4)	MV=1; High flow nasal cannula =2	Coronary artery dilatation n=1; Mitral regurgitation n=1	Nil	Positive RT-PCR (n=4); CRP increased (n=4);	1
32640066	Case report	Bahrami A[13]	1 (0; 1)	5 years	Fever; Abdominal pain; Vomiting; Diarrhea; Conjunctivitis; Rash; Swelling of hands	n=1	IV fluids; IVIG; Acetylsalicylic acid; Epinephrine; Meropenem, Vancomycin, Ciprofloxacin	Nil	Normal	Nil	Lymphopenia; Negative RT-PCR; Positive serology; Thrombocytopenia; Mildly elevated CRP; Hyponatremia; Elevated Procalcitonin & D-dimers	0

33510530	Case report	Rayamajhi A[14]	1 (1; 0)	1 year 5 months	Fever; Rash; Conjunctivitis; Swelling of hands & feet	n=0	IVIG; Aspirin	Nil	Evidence of coronary arteritis	Nil	ND	0
33429476	Brief communication	Lee JH[15]	1 (1; 0)	12 years	Fever; Abdominal pain; Headache; Nausea; Conjunctival injection; Myalgia	n=0	Cephalosporin; IVIG	Nil	Mild MR; Pericardial effusion absent	Nil	Thrombocytopenia; Neutrophilia	0
32788432	Observational study	Jain S[16]	23 (11; 12)	7.2 years	Fever (n=23); Abdominal pain (n=12); Diarrhea/Vomiting (n=15); Breathlessness (n=11); Rash (n=14); Conjunctivitis (n=11); Oral cavity changes (n=4); Limb changes (n=3)	n=15	IVIG; Steroids; Tocilizumab	MV = 9	LV systolic dysfunction = 8; Coronary dilatation = 6	Nil	Neutrophilia; Lymphopenia; Elevated levels of serum ferritin, NT pro BNP & Troponin	1
32462354	Case report	Rauf A[17]	1 (1; 0)	5 years	Fever; Abdominal pain; Diarrhea; Bulbar conjunctivitis; Edema	n=1	Inotropic support; IVIG; Antibiotics; Aspirin; Steroids; Diuretics	High flow nasal cannula	EF=35%; Moderate LV dysfunction; Myocarditis	Nil	Neutrophilic leucocytosis; Elevated levels of CRP, ferritin, ESR, serum creatinine; Hyponatremia; Hypoalbuminemia	0
36438223	Case report	Wang WY[18]	1 (0; 1)	4 years	Fever; Cough; Loss of appetite; Cyanosis; Rash; Bulbar conjunctivitis; Strawberry tongue; Lymphadenopathy	n=0	IVIG; Steroids; LMWH; Aspirin	Nil	Tricuspid regurgitation; EF=65%	Nil	Leucocytosis; Lymphocytopenia; Elevated evels of ESR, Procalcitonin, CRP;	0

											Hypoalbuminemia	
36254726	Observational study	Mamishi S[19]	122 (74; 48)	8.2±4.6 years	Fever (n=105); Headache (n=22); Myalgia (n=21); Conjunctivitis (n=44); Rash (n=50); Cough (n=31); Chest pain (n=4); Tachypnea (n=28); Respiratory distress (n=25); Abdominal pain (n=47); Nausea & vomiting (n=60); Diarrhea (n=39); Sore throat (n=7); Edema (n=19)	n=0	Pulse glucocorticoid therapy; Supportive treatment	Oxygen supplementation (n=26); NIV (n=7); Intubation (n=2)	Coronary artery dilatation (n=42)	n=4	Low levels of Vitamin D	2
33813138	Cross-sectional observational study	Venkataraman A[20]	44 (19; 25)	1-14 years	Fever (n=44); Gastrointestinal symptoms (n=37); Respiratory symptoms (n=11); Mucocutaneous symptoms (n=34)	n=21	IVIG; Steroids; Antibiotics; Toclizumab	HHFNC (n=2); Oxygen (n=7)	Coronary artery dilatation (n=2); Myocardial dysfunction (n=23)	Nil	CRP elevated; Lymphocytosis	0
34413034	Case report	Venkatesha GA[21]	1(1; 0)	12 years	Fever; Vomiting; Diarrhea; Rash	0	IVIG; Pulse steroid therapy	NA	NA	Nil	Elevated inflammatory markers	1
34187796	Case report	Abi Nassif TH[22]	1 (1;0)	8 years	Fever; Generalized edema; Hypotension	0	Vasopressors; Antibiotics; IVIG; Methylprednisolone; Low-dose aspirin	NIV	Carditis; Moderate-to-severe MR; distended IVC	Nil	Anemia; Thrombocytopenia; Elevated inflammatory markers	0

33167916	Observational study	Shahbaznejad L[23]	10 (6;4)	5.37±3.9 years	Fever (n=10); Rash (n=8); Conjunctivitis (n=3); Respiratory symptoms (n=8); Vomiting (n=6); Diarrhea (n=7); Edema (n=6)	2	Antibiotics (n=10); IVIG (n=9); Hydroxychloroquine (n=9); Packed cells (n=7); Albumin (n=7); Steroids (n=2); Infliximab (n=1)	Nil	Abnormal coronary arteries (n=2); Low EF (n=3)	n=2	Anemia (n=8); Thrombocytopenia (n=3); Elevated CRP (n=3)	1
36453214	Observational study	Nadua KD[24]	12 (8;4)	7.5 years	Fever (n=12); Mucocutaneous symptoms (n=12); Headache (n=3)	6	IVIG; High dose steroids; Aspirin; Anakinra; Inotropes	Oxygen support (n=2); Intubation (n=1)	Coronary arteries abnormalities (n=3); Abnormal cardiac function (n=4); Dilated left ventricle (n=2)	Nil	Elevated inflammatory markers	0
34510156	Case report	Al Qahtani M[25]	1 (0;1)	11 years	Fever; Cough; Shortness of breath; Mild abdominal pain; Throat pain; Loss of appetite	1	Antibiotics; Aspirin; IVIG Dexamathasone; LMWH; Tocilizumab	HFNC	Mildly diminished LV function; Dilated coronary arteries	Nil	Elevated inflammatory markers; Lymphocytopenia;	0
32799392	Observational study	Iio K[26]	44 (33;11)	1-4 years	Fever (n=44); Oral changes (n=38); Rash (n=40); Conjunctivitis (n=36); Cervical lymphadenopathy (n=32); Diarrhea (n=9)	0	IVIG; Steroids; Inotropes	Nil	CAA (n-2)	Nil	Positive for anti-SARS CoV-2 Ab (n=2); Elevated inflammatory markers	0

*Abbreviations: IVIG-intravenous immunoglobulins; LMWH-low molecular weight heparin; NIV-non-invasive ventilation; EF-ejection fraction; CAA-coronary artery aneurysm; RT-PCR-reverse transcriptase polymerase chain reaction; CRP-C-reactive protein; MV-mechanical ventilation; MR-mitral regurgitation; HFNC-high flow nasal cannula

Pathogenesis of Multisystem inflammatory syndrome in children:

Multisystem inflammatory syndrome in children has been attributed to be immune mediated by many researchers as it is associated with high levels of inflammatory markers and also responds to immunosuppressive and anti-inflammatory medications. Levels of different cytokines like IL-6, TNF-alpha, IL-10, IL-8, IFN-gamma were found to be elevated in those patients who presented with shock at the time of hospital admission and required vasoactive medications.[20] Levels of phospholipase A_2 enzyme was also found elevated in MIS-C patients when compared to healthy controls; this was a consistent finding in most of the research studies on MIS-C. Decrease in monocyte and dendritic cell subtypes levels was also found consistently in several studies. Majority of patients showed lymphocytopenia with a decrease in T cell counts.[28]

It was observed that children less than 1 year of age have a higher risk of developing COVID-19 infection. Beyond 1-year age, children either remain asymptomatic or may follow a mild course of infection. The severity of infection in children has been linked to their genetic susceptibility and also to having a particular ethnic background. Formation of neutrophil extracellular traps (NETs) which causes cytokine release and activation of immune system in COVID-19 patients, has not been reported to be involved in the pathogenesis of MIS-C. Epidemiological studies carried out in UK, France and USA showed that MIS-C is mediated by activation of acquired immune responses to SARS-CoV-2 infection rather than by a direct viral invasion. Onset of symptoms in MIS-C patients much later than the actual COVID-19 infection; less number of SARS-CoV-2 positive cases and high number of antibody positive cases were the reasons cited by researchers to support the above observation.[29]

The immune dysregulation described in MIS patients was supported by presence of positive serology and negative polymerase chain reaction (PCR) tests in majority of cases. Presence of autoantibodies and immune complexes against different cells in the body like immune cells, endothelial cells of blood vessels and epithelial cells lining the gastrointestinal tract resulted in majority of the patients presenting with vasculitis, gastrointestinal symptoms and fever.[30]

How different is Multisystem inflammatory syndrome in children from Kawasaki disease?

Many of the presenting symptoms of MIS-C resemble those of KD; this has led to clinicians treating MIS-C on the lines of KD. But it has been observed in a study done by Farooqi et al[31] that the diagnostic criteria for KD is rarely met by MIS-C patients; only conjunctivitis and rash being observed in the latter. Patients presenting with lymphocytopenia, relative thrombocytopenia, hypotension, myocardial dysfunction, abdominal pain, diarrhea at an older age favor the diagnosis of MIS-C over KD.[28, 32]

Echocardiography findings in MIS-C mostly shows mild coronary dilatation that occurs during the onset of infection when compared with KD patients where it is of severe type appearing almost 30-35 days of onset of fever. Myocardial dysfunction reverts back to normal in almost all cases of MIS-C by the time the patients are discharged from hospital or when they return for their next follow-up. Asian countries, like China and Japan where KD is prevalent, MIS-C cases were found to be less in number. This difference has been attributed to increase in use of face masks and practice of social distancing that led to decrease in the transmission of most of the common respiratory viruses among the population.[28]

What makes Multisystem inflammatory syndrome in children incidence less common in Asian countries?

When the news on cases of MIS-C were being reported, it was found that these cases were prevalent in Europe and North America. Rarely cases were reported from Asian countries. Was it due to MIS-C being missed by treating pediatricians or was the symptomatology confused with Kawasaki disease? The mystery still remains. Since the outbreak of COVID-19 infection was first reported from Wuhan, China and most of the patients with MIS-C had a prior history of COVID-19 or had positive serology markers for SARS-CoV-2 infection, it was natural to expect higher prevalence and incidence of MIS-C cases in Asian countries when compared to the rest of the world. But this expectation was not met.

Further research helped to postulate few reasons as to why the MIS-C cases were less reported from Asian countries. Firstly, the infection and fatality rates in China was 0.6% and 7.7% respectively. This was less compared to the infection & fatality rates of European countries which was around 9% and 20% respectively. Secondly, genetic and ethnic background differences also contributed to less incidence of MIS-C cases in Asian countries.[33]

In Japan, MIS-C cases were reported during the Delta variant period (10 children were infected) and the Omicron variant period (8 children were infected). The incidence of MIS-C in Japan was also very less compared to that of the

rest of the world. This was in stark contrast to the incidence of Kawasaki disease in Japan whose symptomatology resembled that of MIS-C. Factors that favored less incidence of MIS-C in these patients were genetic predisposition and less prevalence of obesity in such children when compared to hospitalized children of US (obesity rate was 0.8% to 4% in Japan in contrast to 20.9% in hospitalized children of US). Other factors being strict infection control like increased hand hygiene awareness, social and physical distancing, wearing of masks and restriction of activities in public places. All of these reduced the overall incidence of viral and bacterial infections thereby reducing the incidence of MIS-C also.[34]

In a study reported from Singapore during the Delta wave period, it was shown that the number of infected children was more in this wave compared to the early pandemic, the incidence of MIS-C in such patients was also increased.[24]

Treatment protocols followed in Multisystem inflammatory syndrome in children across Asian countries:

The first line of treatment used in MIS-C patients across different Asian countries were IVIG, steroids and antibiotics. Depending on other presenting symptoms, other medications were used.

Study done by Shahbaznejad et al described MIS in 10 febrile children in Iran province. Since all their patients were deficient in Vitamin D and zinc which were also found to have had an immunomodulatory role, supplementation with age-appropriate doses was provided. Few patients also received vasoactive drugs like dopamine and dobutamine based on their conditions.[23]

A study conducted by Jain et al in the city of Mumbai showed that steroids (96%) were used more than IVIG (63%) in treatment of MIS-C patients due to the higher cost of IVIG treatment.[16] This was in contrast to the guidelines issued by National Institutes of Health (NIH) for the management of MIS-C which states that combination of IVIG and steroids offered better immune-protection, faster recovery of cardiac dysfunction and shorter stay in the intensive care unit (ICU).[35]

Conclusion-The way ahead:

Recognition of multisystem inflammatory syndrome in pediatric (MIS-C) cases early in the course of disease and its timely management can greatly reduce the morbidity and mortality associated with it. Symptomatology of MIS-C resembles many other diseases, hence making the clinicians and other health care providers aware of the possibility of MIS-C among such susceptible group can be a step forward in improving the patient's condition. Allowing a platform for relevant discussions related to MIS-C and collaborating with clinicians of other specialties can help in refining management and treatment of the disease.[15]

Vaccination against COVID-19 infection especially with BNT162b2 (Pfizer-BioNTech) has been found to provide increased initial protection in children between 5-10 years. This was the evidence provided by an observational cohort study done in Israel by Amor et al. Based on this it can be postulated that vaccination against COVID-19 can also reduce the incidence of MIS-C.[24] But further studies are required to estimate the duration of this protection.[36]

It has been noted that MIS-C has been less reported from Asian countries. Though this does not rule out MIS-C infection in Asian patients belonging to cohorts from other countries where MIS-C was reported in large numbers. This suggests that further studies need to focus on ethnic, genetic and racial background of patients infected with MIS-C also.

Long term follow-up studies are required to understand the pathophysiology of cardiac complications post MIS-C illness. This would help in improving the management and treatment protocols for such patients in future.[12]

Conflict of interest: the authors declare no conflict of interest.

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