

Leading Article

COVID-19 Related Multi System Inflammatory Syndrome in Children: Spectrum of Kawasaki Disease or Different Entity? A Challenging Mystery for Paediatricians

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Though Paediatric cases account for only about 2.1 to 7.8% of total Covid-19 cases and children are usually asymptomatic or have milder infection,¹ the development of Multi System Inflammatory Syndrome in Children (MIS-C) still remains as one of the most challenging and mysterious issues for the paediatricians.

In April 2020, soon after the first peak of COVID-19, reports from different countries documented a Kawasaki Disease (KD) like hyper-inflammatory syndrome in children in the presence of SARS-CoV-2 infection. This was first diagnosed on 24th April 2020 in The United Kingdom (UK).² Subsequently cases were identified in Europe, USA and other countries³⁻⁷ These patients had hyper inflammatory shock with features similar to Kawasaki Disease (KD) and toxic shock syndrome (TSS).

The Royal College of Paediatrics and Child Health referred to this acute condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).⁴ A temporal association with SARS-CoV-2 infection had been hypothesized because some children tested positive for the virus, either by RT-PCR or serology or had potential family contact with COVID-19 case. MIS-C is reported to present with persistent fever and a constellation of symptoms including hypotension, multi-organ (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic) involvement, and elevated inflammatory markers.⁵⁻⁷ Patients tested positive for SARS-CoV-2 by RT-PCR reflect an acute phase of the infection, although the virus or its fragments may be detected for longer periods in some patients and could also be responsible

for these results.⁸ However, it is not clear how long it might take for the first symptoms of MIS-C to appear after the acute phase of SARS-COV-2 infection, and whether it may occur during the acute phase or not. But most of the reports document that MIS-C manifests 3 to 4 weeks after SARS-CoV-2 infection.^{2,9,10} Children with severe MIS-C are reported to have higher levels of antibody response to SARS-CoV-2.^{11,12}

There were dilemmas in the nomenclature of this new syndrome due to the severity and much similarities with KD. Different terminologies of this syndrome included: Kawasaki like syndrome (KLS), atypical Kawasaki Disease, incomplete Kawasaki Disease, hyperinflammatory shock, Kawa-Covid- 19, SARS-CoV-2-induced Kawasaki like hyperinflammatory syndrome (SCiKH syndrome), MIS-C and PIMS-TS.³ Later, the illness was labeled as multi system inflammatory syndrome in children (MIS-C) by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC).^{3,13}

Preliminary case definition of MIS-C (a) by WHO³ is based on six principle features:

- Children and adolescents 0–19 years of age with fever > 3 days
- Evidence of multisystem (>2) organ involvement (cardiac, kidney, respiratory, haematologic, gastrointestinal, dermatologic, or neurological)
- Evidence of a recent infection by SARS-CoV-2 (positive RT-PCR, serology, or antigen test) or COVID-19 exposure within 4 weeks prior to the onset of symptoms.
- Presence of at least one of the following laboratory abnormalities: elevated CRP level, ESR, fibrinogen, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes; and low albumin.
- No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

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Patients who meet the case definition criteria of MIS-C may have three different clinical presentations:^{7,14}

- I. Febrile inflammatory state/ Persistent fever and elevated inflammatory markers: These patients do not have feature of organ dysfunction, KD or shock.
- II. Kawasaki disease (KD) like illness (having features of complete or incomplete KD) and
- III. Severe MIS-C where cardiac involvement, collapse and shock are common.

It is unclear whether the immunological mechanisms behind hyper inflammation on MIS-C are the same as that in adults with COVID-19. Cytokine storm induced hyperinflammation is usually seen in first two weeks, but MIS-C is commonly reported after 2 to 4 weeks of SARS-CoV-2 infection. The pathogenetic basis for MIS-C is the dys-regulation of the innate immune response, and as a result there is an excessive production of pro-inflammatory cytokines, leading to cytokine storm.

A debate is still going on among pediatric rheumatologists and immunologists, whether MIS-C and KD are part of the same disease spectrum or represent different disease? There are similarities and dissimilarities between the two conditions.¹⁵⁻¹⁷

Similarities include: persistent fever with self-limited course, irritability, cervical lymphadenopathy, conjunctival ingestions, lip and oral changes, skin rashes and development of coronary artery aneurysms. Treatment of the two conditions are also similar including use of Intra Venous Immunoglobulin (IVIG), glucocorticoids and other immunomodulators in resistant cases.

Dissimilarities are reported as higher age distribution of MIS-C cases, high frequencies of signs and symptoms that are unusual in KD including GI symptoms, myocardial dysfunctions and CNS involvement. As compared to KD, MIS-C is marked by more intense inflammation evidenced by markedly raised ESR, CRP, ferritin and procalcitonin, development of shock and to some extent MAS. Thrombocytopenia and lymphopenia is quite common in MIS-C which are very rarely found in KD.¹⁵⁻¹⁷ Marked elevation of myocardial markers including pro-BNP and Troponin are common in MIS-C. Evidence of coagulopathy (by PT, PTT, elevated D-dimers) are also markedly raised in MIS-C. Moreover, Ethnicity also differs in two conditions. KD is more common in

North-East Asian countries, whereas MIS-C is reported commonly in Black, Hispanic and Latin children.¹⁸ However, Middelburgh et al. in their report from Netherlands showed that Black children are 15 times more likely to develop COVID-19 related MIS-C than White children and Asian children are 11 times more likely and other non-White children do not have substantial high risk.¹⁹

Kostik et al. in a retrospective multicenter study in Russia tried to develop a scoring system (KMD score) to distinguish between MIS-C and KD.²⁰ Five criteria were included in the KMD score and were given certain points:

- i. CRP > 11 mg/dl (18 points), ii. D-dimer > 607 ng/ml (27 points), iii. Age > 5 years (30 points) iv. Thrombocytopenia (25 points), and v. GI involvement (28 points)

A total score >55 strongly allowed to discriminate MIS-C from KD with a sensitivity of 87.5% and specificity of 89.1%.²⁰

In spite of all, some authors still favour the hypothesis that MIS-C is on the KD spectrum, instead of representing a new entity¹⁵. They do also have strong arguments and justifications behind their belief. Only time and further studies with clarifications may prove or discard the hypothesis.

According to CDC (January 03, 2022), in the USA the total MIS-C cases were 6,431 and total MIS-C deaths were 55.⁵ In the Department of Paediatrics (Rheumatology Division), Bangabandhu Sheikh Mujib Medical University, we have so far, experienced more than 64 cases of MIS-C. Majority of our cases presented with KD like illness followed by severe MIS-C. Severe MIS-C cases presented with KDSS, shock, respiratory failure, hepatitis, pneumonia, heart failure, encephalitis and appendicular rupture. Only five MIS-C cases presented with mild illness (febrile inflammatory state). An outpatient based prospective study done in BSMMU over a period of 4 months (April 2020 to July 2020) showed that among 377 total COVID 19 cases, all the 298 mild cases (100 %) and 11 of 58 moderate COVID-19 cases were managed in the outdoor²¹. So, it is quite possible that mild MIS-C cases were not identified by investigating the markers and were managed in the OPD and thereby not referred to us.

As reported elsewhere, we also had fever followed by GIT, muco-cutaneous, cardiovascular and respiratory symptoms as presenting features. About 34% patients from our center were discharged with sequelae, mostly

cardiac related. We lost 4 MIS-C cases in spite of taking all the available measures. All of them had known co-morbidities including primary immune deficiency disorders (X-LA) in 2 cases and systemic lupus erythematosus with organ involvements in 2 other cases. Initially, when serological test for SARS-CoV-2 infection was not available, we had to depend on positive RT-PCR (infrequently present) and history of close contacts, which also may have been missed. Even now serological test is not widely available. Moreover, as because MIS-C cases may have variable presentations, there is a strong possibility of missing these cases, if very high index of suspicion is not present. We tried to follow the American College of Rheumatology (ACR) guidelines (version 1),²² but it was not always possible to adhere to the guidelines because of logistic constraints. As because Intravenous immunoglobulin (IVIG) is very expensive, it was not always possible to manage.

School children > 12 years in our country are advised to take vaccines against COVID-19 and free vaccines are being provided by Government of Bangladesh. Special Guidelines and recommendations about vaccination regarding MIS-C are available in the website of European Society of pediatric Rheumatology (PReS).²³ Based on several studies PReS recommends that: the benefits of COVID-19 vaccination following MIS-C outweigh the theoretical risk of new MIS-C.

PReS along with other international societies are actively collecting information on MIS-C cases including those children who were vaccinated with the COVID vaccines after recovery from MIS-C; So far, the data demonstrates safe outcome. Following MIS-C, it is recommended to vaccinate after 6 months, following full clinical recovery, and normal cardiac function. If IVIG was not given as MIS-C therapy, vaccination may be considered after 3 months. But, for children who had MIS-C following COVID vaccine, it is recommended to withhold further vaccination.²³

The international registry on COVID-19 related hyperinflammation in children and young adults (HyperPED-COVID) is a coordinated international action involving PReS, European Society for Immune Deficiencies (ESID), International Society for Systemic Autoinflammatory Diseases (ISSAID), European reference Network – rare Autoinflammatory and Autoimmune Diseases (RITA-ERN) and Pediatric Rheumatology International Trial Organisation

(PRINTO). They are collecting data of patients with MIS-C and will also include the same on the safety and efficacy of SARS-CoV2 vaccines in these patients.

From Bangladesh, as approved authority, we are uploading information related to MIS-C cases using the website. When this international registration data will be analyzed in near future, it is expected that, many unresolved issues including vaccination would be solved and much more clear idea about different aspects of MIS-C related to COVID-19 will be available to us.

In conclusion, MIS-C is still a mysterious issue and remains a challenging paediatric emergency observed during COVID-19 pandemic. Early diagnosis and referral to tertiary center for optimum management is essential. A strong index of suspicion should be present for early diagnosis and management of MIS-C cases. Children with pre-existing co-morbidities are much more vulnerable and their families should be extra careful to protect these children. A pragmatic approach in the management of MIS-C focusing on low-income countries like us is also very much needed, as majority of our patients cannot afford expensive investigation panel for diagnosis and treatments including IVIG.

References:

1. Centers for Disease Control and Prevention (CDC), USA. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). 2020; <https://www.cdc.gov/mis-c/hcp/R>
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; 395(10237):1607-1608. doi: 10.1016/S0140-6736(20)31094-1.
3. World Health Organisation. Multi System Inflammatory Syndrome in Children and Adolescents with COVID-19: Scientific brief, World Health Organisation. 2020; 15 May. <https://apps.who.int/iris/handle/10665/332095>.
4. Royal College of Paediatrics and Child Health. Guidance: Paediatric Multisystem inflammatory syndrome temporally associated with COVID-19. Londres (Royaume-Uni) 2020.
5. Centers for Disease Control and Prevention. Health Department-Reported Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) in the United States. Retrieved on 3 February, 2022; <https://www.cdc.gov/mis-c/cases/index.html>
6. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 Pediatric Patients: A Systematic Review. *EClinicalMedicine* 2020; 24:100433. doi: 10.1016/j.eclinm.2020.100433.
7. Whittaker E, Bamford A, Kenny J, Kafrou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020; 324(3):259-69. doi: 10.1001/jama.2020.10369.

8. John G, Sahajpal NS, Mondal AK, Ananth S, Williams C, Chaubey A, et al. Next-Generation Sequencing (NGS) in COVID-19: A Tool for SARS-CoV-2 Diagnosis, Monitoring New Strains and Phylodynamic Modeling in Molecular Epidemiology. *Curr. Issues Mol* 2021; 43(2):845-67. <https://doi.org/10.3390/cimb43020061>
9. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, et al. Multisystem Inflammatory Syndrome in US Children and Adolescents. *N Engl J Med* 2020; 383(4):334-46.
10. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem Inflammatory Syndrome in Children: A Systematic Review. *EClinical Medicine* 2020; 100527. <https://doi.org/10.1016/j.eclinm.2020.100527>
11. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, et al. Quantitative SARS-CoV-2 Serology in Children with Multisystem Inflammatory Syndrome (MIS-C). *Pediatrics* 2020; 146:e2020018242.
12. Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, et al. A Human Neutralizing Antibody Targets the Receptor-Binding Site of SARS-CoV-2. *Nature* 2020; 584:120-124. <https://doi.org/10.1038/s41586-020-2381-y>.
13. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children. Available from: <https://www.cdc.gov/mis-c/index.html>
14. Son MBF, Friedman K. Coronavirus disease 2019 (COVID 19). Multisystem Inflammatory syndrome in children. Up to date 2020; <https://www.uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-clinical-features-evaluation-and-diagnosis>
15. Matucci-Cerenic C, Carosi R, Consolaro A, Rosina S, Civino A, Ravelli A. Multisystem Inflammatory Syndrome in children: Unique Disease or Part of the Kawasaki Disease Spectrum? *Front. Pediatr* 2021; 9:680813. Doi: 10.3389/fped
16. Zhang Q Y, Xu B W, Du JB. Similarities and Differences Between Multiple Inflammatory Syndrome in Children Associated with COVID-19 and Kawasaki Disease: Clinical Presentation, Diagnosis, and Treatment. *World Journal Pediatrics* 2021; <http://doi.org/10.1007/s12519-021-00435-y>
17. Kabeerdoss J, Paliana RK, Karkhle R, Kumar TS, Danda D, Singh S. Severe COVID-19, Multisystem Inflammatory Syndrome in Children, and Kawasaki Disease: Immunological Mechanisms, Clinical Manifestations and Management. *Rheumatology International* 2021; 41; 19-32.
18. CDC. Multisystem Inflammatory Syndrome in Children (MIS-C). Centers for Disease control and prevention 2020; <https://www.cdc.gov/mis-c/hep/>.
19. Middelburgh JG, Crijnen TEM, D'Antiga L, Verdoni L, Chikermane A, Gaeg P et al. Association of Ethnicity with Multisystem Inflammatory syndrome in Children Related to SARS-CoV-2 Infection: An International Case-Referent Study. *Front. Pediatr* 2021; 9: 707650. Doi: 10.3389/fped.2021.707650.
20. Kostik MM, Bregel LV, Avrusin IS, Dondurei EA, Matyunova AE, Efremova OS et al. Distinguishing Between Multisystem Inflammatory Syndrome, Associated with COVID-19 in Children and the Kawasaki Disease: Development of Preliminary Criteria Based on the Data of the Retrospective Multicenter Cohort Study. *Front. Pediatr* 2021; 9: 787353. doi: 10.3389/fped
21. Haque M, Laila K, Al-Mamun MH, Supti SH, Rahman SA. Profile and Outcome of Children with COVID-19 Attending Bangabandhu Sheikh Mujib Medical University. *American J. Pediatrics* 2021; 7(2):72-8. doi: 10.11648/j.ajp.20210702.17 ISSN: 2472-0887 (print); ISSN: 2472-0909 (Online)
22. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, Behrens EM, Ferris A, Kernan KF, Schulert GS, Seo P, F Son MB, Tremoulet AH, Yeung RSM, Mudano AS, Turner AS, Karp DR, Mehta JJ. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. *Arthritis Rheumatol* 2020; Nov 72(11):1791-1805. doi: 10.1002/art.41454. Epub 2020 Oct 3. PMID: 32705809; PMCID: PMC7405113.
23. PReS Recommendation for COVID 19 Vaccination. Guidelines and Recommendations: PReS Update Regarding COVID-19 Vaccination in Children with Rheumatic Diseases. December 2021; *Vaccines and MIS-C*.