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Editorial

Emergence of MIS-C in COVID-19 pandemic

Mehnaaz Sameera Arifuddin

Department of Physiology, Deccan College of Medical Sciences, Kanchanbagh, Hyderabad-500058, Telangana, India.

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The COVID-19 pandemic will be seen in future as an authentication to the insatiable nature of evidence-based medicine. Many clinical trials and research studies have shown that there is a greater impact of this disease in adults with children having escaped its severity **[1]**. Worldwide there has been a decline in the number of cases of COVID-19. Simultaneously, there have also been reports of multisystem inflammatory syndrome in children (MIS-C) with clinical presentation similar to Kawasaki disease (KD) 4-6 weeks post COVID-19 infection **[2]**. Fever, enlarged lymph nodes, skin rash, increase in inflammatory biomarkers are common to both these conditions suggesting a genetic predisposition **[3]**.

Kawasaki disease occurs as a result of an infectious trigger in genetically susceptible individuals of East Asian descent. However in MIS-C the trigger seems to be COVID-19 infection that results in a cytokine storm among children during the recovery phase **[1]**. Jones et al first reported in April 2020, a case of 6 month old infant with fever and respiratory symptoms later diagnosed as Kawasaki disease with positive RT-PCR for SARS-CoV2 infection **[4]**. Many such cases have been reported till date worldwide.

SARS-CoV2 belongs to the β species of coronaviruses family. It spreads through close contact with affected patients and also gets transmitted via contaminated surfaces. It requires angiotensin converting enzyme-2 (ACE-2) receptor to gain entry into human body; this receptor is widely located in pulmonary and cardiac epithelial tissues, vascular endothelial cells, and alveolar cells in the lungs **[5]**. The severity of the infection depends on the extent of innate immune dysregulation and consequent cytokine storm. Granulocytes, especially Neutrophils kill invading microorganisms by phagocytosis and initiate an innate immune response. Among the various functions of neutrophils, one of them is to form neutrophil extracellular traps (NETs) which contain cell-free DNA, histone proteins, and microbicidal enzymes. Many microorganisms including viruses stimulate the formation of NETs which serve dual function. Not only do they serve to trap the virus, they can also initiate uncontrolled inflammatory and immunological reactions in the host resulting in hyper inflammatory response similar to that seen in MIS-C **[6]**. Another study has shown that the increased plasma level of NETs in SARS-CoV2 patients correlates with the severity of COVID infection. NETs also promote coagulation but further evidence is required to understand their role in abnormal coagulopathy observed in MIS-C patients **[7]**.

Clinical presentation of MIS-C is usually delayed when compared to the pandemic curve. Lab investigations confirm that among those infected, a low proportion of cases were SARS-CoV2

Corresponding author
Dr. Mehnaaz Sameera Arifuddin
Associate Professor
Department of Physiology, Deccan College of Medical Sciences, DMRL 'X' Road, Kanchanbagh, Hyderabad-500058, Telangana, India.
Phone: +91-9963850393
Email: mehnaaz@deccancollegeofmedicalsciences.com

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positive, and a high proportion were antibody positive suggesting that this inflammatory syndrome corresponds to initiation of acquired immune responses against SARS-CoV2 and not due to direct viral invasion. Another clinical finding common to MIS-C and Kawasaki disease is the formation of coronary aneurysm. The plausible mechanism involved is injury to heart and coronary arteries through immune complexes formed as a result of coronavirus infection.

Since MIS-C cases fulfilled the diagnostic criteria of Kawasaki disease, these patients were managed with standard protocol for Kawasaki disease. Management includes administration of intravenous immunoglobulin, aspirin, steroids, immune-modulators, and supportive care in cases associated with shock syndrome. Role of Remdesevir in treatment remains controversial as children reporting with MIS symptoms are not in the acute phase of illness; and since remdesevir inhibits the active viral replication, use of this drug in treatment of MIS-C is limited **[5]**.

Emergence of MIS-C cases has drifted the attention of scientific community towards possible complications post SARS-CoV2 infection which can contribute to increased mortality and morbidity. Hence, it remains to be seen how future clinical trials provide conclusive evidence on the pathophysiology and immune response mechanisms of MIS-C which can later be used to develop effective treatment protocols including SARS-CoV2 vaccines.

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