EDITORIAL

Multisystem Inflammatory Syndrome of Children Related to SARS-CoV-2: A Novel Experience in Children with a Novel Virus

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Abstract

Severe acute respiratory syndrome-coronavirus-2 (SARS CoV-2) is a novel virus. There has been an increasing number of case reports on multisystem inflammatory syndrome in children (MIS-C) but the global and population-specific incidence of MIS-C particularly in Asian countries, its causal relationship with SARS-CoV-2 and its immunopathogenesis remain unknown. Emerging questions on how the pathophysiology of MIS-C differs from that of Kawasaki disease (KD) and non-KD inflammatory syndromes need to be answered. Genetic factors influencing the incidence of MIS-C in the different ethnic populations are to be explored. What happens to the children with MIS-C, in the long run, remains unknown to date. Multicenter clinical trials are needed to establish optimal treatment and follow-up for MIS-C.

Keywords: Kawasaki disease, Multisystem inflammatory syndrome in children, SARS-CoV-2.

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Cases of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pneumonia were reported from the Wuhan province of China in December 2019 and in March 2020, the World Health Organization (WHO) declared it a pandemic. Children were considered to be either asymptomatic or minimally symptomatic with SARS-CoV-2 with no potential short- or long-term complications. In April 2020, a mysterious but rare syndrome mimicking Kawasaki disease (KD) was first reported in children in the UK. Similar constellations of clinical and laboratory parameters in children were soon getting reported from different parts of the world except Asia and a temporal association with SARS-CoV-2 was gaining momentum. The current article in IJCCM titled "Multi System Inflammatory Syndrome in Children: Clinical features and Management-Intensive Care Experience from a Paediatric Public Hospital in Western India" by Lakshmi Shobhavat et al.[1] is a welcome addition to the evolving world literature on the subject in the Asian context.

Centre for Disease Control and Prevention (CDC), USA named it multisystem inflammatory syndrome in children (MIS-C); Royal College of Pediatrics and Child Health (RCPCH), UK called it pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and WHO referred to it as a pediatric multisystem inflammatory syndrome (PMIS). A similar condition in adults was reported as MIS-A in a new CDC study.[2]

Increased mortality and morbidity following SARS-CoV-2 were reported in MIS-C and MIS-A. It assumed increasing public health importance over time. Globally, parents found it very difficult to accept the sudden diagnosis of a life-threatening complication weeks after the child had recovered from SARS-CoV-2. Clinicians were divided in their opinion on how best to diagnose and manage this condition, what to expect afterward following recovery, how to follow-up, and what to look for as potential future consequences of MIS-C in the survivors.

Thanks to months of research, what began as a mysterious spectrum of symptoms has coalesced into a definable illness[3] called MIS-C with its characteristic features defined by WHO, RCPCH (UK), and CDC (USA). However, the pathophysiology of MIS-C, its exact immune mechanisms (e.g., autoantibody production; cytokine release syndrome; dysregulated bradykinin signaling; "Staphylococcal Enterotoxin B" like super-antigenicity of viral spike protein) and its temporal association with SARS-CoV-2 are still being evaluated.

MIS-C share features with typical or atypical KD and other non-KD inflammatory conditions in children.[4] Diagnostic confusion initially led some clinicians to believe that the two conditions were the same.[5] Kawasaki disease is seen primarily in children below 5 years, while MIS-C tends to affect older children and adolescents up to 21 years of age.[6] The median age of the current study cohort was 7 years with 43% having left ventricular dysfunction and 24% having dilatations of the coronary artery. It is too early to define the pathological mechanism of coronary artery dilation seen in MIS-C with certainty, but an endothelial dysfunction sustained by the cytokine storm could be a likely one.[7]

CDC recently published initial findings of around 600 children in the USA who fit its broad case definition of MIS-C. Class 1 with the highest degree of organ involvement, higher prevalence of shock, and lymphopenia with little overlap with KD had true MIS-C. Class 2 had the most respiratory symptoms and highest reverse transcription polymerase chain reaction (RT-PCR) positivity for

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SARS-CoV-2 and likely had acute corona virus disease-19 (COVID-19). Class 3 more commonly met the criteria for KD. SARS-CoV-2 can affect multiple organ systems but the presence of multiple organ involvement does not necessarily indicate a diagnosis of MIS-C.[8]

Pathogenesis of MIS-C and KD is unknown, and a hypothesized post-infectious etiology is not proven. The virus is generally not detected in the respiratory tract of patients with MIS-C.[9] Analysis of 662 cases of MIS-C by Moreira et al. showed the development of MIS-C several weeks after the classic signs of the SARS-CoV-2 appeared in children or after an asymptomatic infection.[10] Standard tests confirming the presence of the virus often come back negative by the time MIS-C manifests. MIS-C and MIS-A had gastrointestinal (GI) symptoms in 80–90% of cases globally, 38% of positive RT-PCR; 76% positive antibody test; only 40% with respiratory illness though SARS-CoV-2 is known primarily as a respiratory pathogen; 100% with fever and 76% with GI symptoms (e.g., severe abdominal pain, nausea, diarrhea, vomiting) in the current study cohort matched world literature on MIS-C. Siew Ng proposed a stool test for the virus in children with MIS-C negative for the virus and implied that SARS-CoV-2 may continue to replicate in the GI system for months causing severe gut dysbiosis.[11–13] The role of remdesivir in the treatment of MIS-C is therefore limited as most children with MIS-C are not in the acute phase of illness and the virus is not detectable by RT-PCR in many.

Severe acute respiratory syndrome-coronavirus-2 spikes binding to mucosal angiotensin converting enzyme-2 (ACE2) receptors have motif sequence and structure homology to Staphylococcal enterotoxin B (SEB), considered a superantigen[11] which could mediate the overwhelming cytokine and bradykinin storm leading to shock requiring fluid and inotrope support in as many as 90% children with MIS-C in the current study.

Treatment of MIS-C is mostly supportive preferably in a paediatric intensive care unit (PICU) set up by a multidisciplinary team (MDT) with intravenous immunoglobulin (IVIG), steroid, biologics—Anakinra/anti-IL-1Ra and tocilizumab/anti-IL6, aspirin, low molecular weight heparin, antibiotics, and remdesivir either alone or in combination while correcting shock and hypotension with fluid and inotropes with or without mechanical ventilation.

The role of IVIG and steroids in managing MIS-C is still being evaluated and debated. The current study reported the use of pulse methylprednisolone in 85%, IVIG in 52%, and tocilizumab in 19%. The use of steroids in 85% is much higher compared to its much lower use in western centers. IVIG recommended by the majority (70%) of the centers in the west as the primary immunomodulator should ideally work as autoantibody production is considered a probable mechanism for MIS-C. The cost of IVIG may be prohibitive in a resource-limited setting. RECOVERY trial showed that steroids might reduce death by a third in patients with severe SARS-CoV-2 on a ventilator. As a potent anti-inflammatory agent, it is a cheap and more accessible alternative to IVIG but their potential to induce broad immunosuppression might be hazardous and its use needs to be restricted.

There is no consensus on which of these agents or treatment strategy is optimal, and the choice of drug depends on clinician preference, cytokine panel results, and availability. MIS-C has been reported in low- and middle-income countries (LMICs) with western literature highlighting its prevalence among the disadvantaged socioeconomic class. Many of the therapeutic agents used to treat MIS-C are unavailable or unaffordable in most LMICs and therefore the choices for immunomodulation are limited. Randomized clinical trials (RCTs) are needed to establish which treatment is beneficial and effective. Close follow-up by MDT is very important as the natural history of MIS-C is still unclear. Hope that an effective vaccine will be there on the horizon soon.

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