State of the Globe: Multisystem Inflammatory Syndrome in Children – Did the COVID-19 Pandemic Actually Handle Kids with Kids-Glove?

The world is witnessing unprecedented mayhem at the hands of a novel mutation in coronavirus since December 2019. Globally, as of November 22, 2021, there have been 256,966,237 confirmed cases of COVID-19, including 5,151,643 deaths, reported to the WHO.[1] Although the WHO site does not give age-wise distribution of cases, it was found that out of total only about 12.3% cases were below the age of 18 years in the survey done in US in March 2021. Further only 1 in 20 cases fell in the severe category in children as compared to up to 1 in 5 falling in the severe category from the adult population.[2] Hence, early during the course of pandemic, the onslaught on children was considered to be mild as they were susceptible to lower transmission rates and lower severity even if exposed to the infection.

However, a new disease entity, with symptoms encompassing the spectrum of Kawasaki disease (KD) at one end and KD with shock syndrome (KD with SS) and macrophages activation syndrome at other end, reported in children infected with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) virus 3–6 weeks previously shifted our paradigm of understanding the impact of coronavirus upon children.[3] It was named as multisystem inflammatory syndrome in children (MIS-C) as many of the clinical features were found to be distinct, although sharing many inflammatory pathways with these diseases. The disease affects many organs of the body by a mechanism known as antibody-dependent enhancement. This is differentiated from the hyper-inflammation or cytokine storm seen in the acute phase of coronavirus infection as most of the children affected show evidence of past infection and absence of reverse transcription polymerase chain reaction (RT-PCR)-based evidence of current or active infection.[4] The triggering factor of this postinfectious inflammatory dysregulation is still under investigation while some predisposing factors such as host genetic predisposition and role of oxidative stress have been postulated.[5,6] Sethy *et al*. have explored the clinical and demographical profile of the disease with its outcome in children, in their multi-centric retrospective analysis of children presenting with MIS-C to the contributory hospitals, published in this issue.[7]

Diagnostic criteria have been laid by CDC and WHO separately for helping out physicians identify this challenging disease.[8] The presence of fever and raised inflammatory markers is common among both of these criteria. CDC lays all the four criteria to be met for diagnosing MIS-C in children below 21 years age, fever documented to be above 38°C, raised inflammatory markers (C-reactive protien, erythrocyte sedimentation rate, fibrinogen, pro-calcitonin, D-dimer, ferritin, etc.) along with the absence of any other plausible cause and severity enough to cause hospitalization in a child having evidence of infection/exposure within 4 weeks before illness or contact with person with exposure to the virus. Similarly, the WHO criteria also rely on documented or perceived fever and inflammatory markers elevation along with clinical evidence of organ dysfunction such as cardiac abnormalities, coagulopathy, or gastrointestinal manifestations such as vomiting and/or diarrhea and evidence of infection in the past. The exclusion of all other diseases such as bacterial sepsis, staphylococcal or streptococcal SS is necessary for fulfilling the criteria. Prominent among other clinical features are gastrointestinal symptoms and pain abdomen, bilateral conjunctivitis, and rashes along with the varying degree of involvement of lungs, liver, kidneys, heart, and central nervous system. In view of high morbidity and mortality in the absence of proper management, a multidisciplinary approach has to be adopted for prompt diagnosis and management of the suspected cases.[8]

Considering the urgency of making a diagnosis on one hand and avoiding over-diagnosis on other, a step-wise approach is recommended for ordering the investigations after clinical suspicion. It is preferable to include a pediatric rheumatologist along with cardiologist, pediatric intensivist, and infectious disease expert, to plan the course of investigations and management, whenever possible. This includes tier 1 and tier 2 of investigations along with hospital admission and intensive care unit transfer of acutely sick children while they are undergoing investigations as per the set protocols. Tier 1 investigations include routine complete blood count with differential count, renal and liver function tests, SARS-CoV-2 by RT-PCR, and assessment of other sources of fever. If no other cause of fever is ascertained and child continues to show severe manifestations along with persistent fever tier 2 of investigations should include ESR, procalcitonin, interleukin-6, ferritin, troponin NT-proBNP, electrocardiogram, coagulation studies, and SARS-CoV-2 serology. Cardiological investigations and radiological imaging should be included whenever required.[9]

Clinical and laboratory features of MIS-C, KD, and KD with SS overlap, suggesting common inflammatory pathways. However, some distinction can be made, based upon the age of presentation, which is higher in children with MIS-C, whereas infants and younger children are the usual victims of KD. CRP

and other inflammatory markers are much higher in MIS-C as compared to KD and KD with SS. Total platelet counts in MIS-C tend to be lower than normal, while it is normal to elevated in KD and KD with SS.[10]

Treatment guidelines have been reviewed extensively by the WHO. In its latest update on November 23, 2021, of clinical guidelines for the management of children aged 0 −18 years with MISC and those with MISC and KD, the WHO has recommended the use of corticosteroids and supportive care in the former while corticosteroids and IVIG along with supportive care in latter.[4] Anakinara has also been used in refractory cases.[11] Overall, the prognosis after proper management is reasonably good, although monitoring of systemic functions and repeat ECHO to assess myocardial involvement and coronary artery aneurysms are required.[12]

Henceforth, although only 1 in 1250 SARS-CoV-2-infected children required hospital admission during the acute stage, additional 1 in 4100 children developed serious and potentially lethal complication, i.e., MIS-C postinfection.[13] CDC has reported 5526 cases of MIS-C with 48 deaths till November 1, 2021.[14] Hence, considering the higher severity and mortality associated with MIS-C and absolute number of children having exposure to coronavirus, it is no longer prudent to label COVID-19 pandemic impact upon the pediatric age group as mild even if we disregard the psychosocial and educational hardships faced by them.

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