

COVID-19-related cytokine and information storm: considerations regarding multisystem inflammatory syndrome in children

The article on coronavirus disease 2019 (COVID-19) related multisystem inflammatory syndrome in children reporting two clinical cases, published in this issue by Taffarel et al., describes the association of COVID-19 infection and critical disease in pediatric patients. In children, clinical manifestations of COVID-19 infection are usually mild to moderate; however, notwithstanding its low prevalence, multisystem inflammatory syndrome (MIS) should be taken into account due to its severity.¹ Further knowledge regarding MIS based on clinical features, severity-associated factors, and therapeutic interventions, as described in the article, is essential for timely diagnosis and early treatment. Therefore, the case reports and literature review provided by the authors are extremely helpful in our daily clinical practice. Interestingly, as mentioned in the study, although these patients are critically ill, mortality rate is low.

The overwhelming information on COVID-19 and the syndrome considered here (MIS) has led us to reflect on different aspects that, according to our understanding, should be mentioned in order to avoid possible confusion. In this regard, the first consideration is the relation between MIS and the clinical characteristics it has in common with Kawasaki disease (KD).²

European studies have reported a 30-fold increased incidence of KD compared to historical (pre-pandemic) data from the same time of year.³ These patients with KD (who meet the diagnostic criteria) did not present with features that were different from those widely known for KD. Nevertheless, there is a subgroup of older patients (>5 years) with more frequent gastrointestinal and neurological manifestations, myocarditis, hemodynamic failure, and abnormalities on laboratory tests (lymphopenia, thrombocytopenia, increased ferritin levels) associated with a more severe presentation, termed atypical KD.^{4,5} This subgroup of patients with KD is more likely to develop Kawasaki shock syndrome (approximately 10 % will develop KSS) or a phenotype similar to toxic shock syndrome.⁶ These two conditions share clinical and biochemical features with MIS. In addition, 25 % of patients defined as having MIS may meet the

diagnostic criteria for KD, although in some series up to 50 % of patients with MIS were shown to meet these criteria. It may be hypothesized that race, ethnicity, and epigenetics play a role in the virus-host interaction leading to the development of one phenotype or the other.

The cause of such severe presentations is unknown; however, some studies suggest involvement of the pathophysiology. Activation of the immune system by the presence of an antigen initiates a process that starts with antigen presentation by antigen-presenting cells (APC) to CD8+ and NK cells that produce inflammation through cytokine and chemokine secretion activating the innate immune system and subsequently the adaptive immune system. Nevertheless, when viral mechanisms of immune evasion are involved, a loss of balance may lead to immune dysregulation resulting in the persistence of antigens due to a lack of viral clearance, an exaggerated immune response to the stimulus, and persistent inflammatory cells producing proinflammatory cytokines, including tumor necrosis factor alpha (TNF- α), interferon-gamma, interleukin 1 (IL-1), interleukin 6 (IL-6), and interleukin 18 (IL-18), among others.

Perpetuation of this event is accompanied by the activation of macrophages that provide feedback to the response by producing the macrophage inflammatory protein (MIP)-1 beta.⁷ Altogether, this leads to the so-called cytokine storm, reminiscent of conditions such as familial hemophagocytic lymphohistiocytosis (FHL) and macrophage activation syndrome (MAS) or others gathered under the umbrella term "cytokine storm syndrome", including acute respiratory distress syndrome, malignancy-associated syndromes, and infections, such as Epstein-Barr virus (EBV) and influenza and, currently, COVID-19 as a new infectious agent capable of triggering such a cytokine storm.⁸

Another aspect to take into account is the temporal relationship between the infection and the development of MIS. As described in the study by Taffarel et al., a history of infection within the previous 2-6 weeks is commonly found in the literature. Evidence of a current or past reactive infection should therefore also be

considered in the therapeutic decision-making.

To date, there are no relevant data on underlying pediatric conditions or diseases that would predispose to or facilitate the development of MIS. As to severity, approximately 40 % of the patients were admitted to the intensive care unit (ICU); the mean length of hospital stay was 5 days; and in 80 % of the patients shock involved more than two organs, similar to septic shock and thus suggesting the need for initial management of critically ill patients by specialized healthcare professionals.⁶⁻⁹

Only low-level evidence is available on treatment, consisting of case reports, consensus statements, and expert guidelines; therefore, no conclusions can be drawn regarding effectiveness and safety. Nevertheless, given the lack of robust evidence and controlled studies and considering similarity to well-known diseases in which efficacy of certain treatments has been demonstrated, the use of intravenous gammaglobulin (IVGG), corticosteroids, and biological agents should be evaluated in the process of decision-making in the interdisciplinary team managing critically ill patients with MIS.¹⁰

Further knowledge on and awareness of this disease as well as the creation of specialized teams in charge of decision-making and the development of guidelines (or adaptation of existing ones) to be used in our setting are key points that will allow for improved quality of care for critically ill children with MIS by pediatricians.

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