EDITORIAL

Childhood Multisystem Inflammatory Syndrome — A New Challenge in the Pandemic

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The recognition and description of new diseases often resemble the parable of the blind men and the elephant, with each declaring that the part of the beast they have touched fully defines it. As the coronavirus disease 2019 (Covid-19) pandemic has evolved, case reports have appeared describing children with unusual febrile illnesses that have features of Kawasaki's disease,[1] toxic shock syndrome,[2] acute abdominal conditions, and encephalopathy, along with other reports of children with fever, elevated inflammatory markers, and multisystem involvement.[3-5] It is now apparent that these reports were describing different clinical presentations of a new childhood inflammatory disorder.

A case definition for the emerging disorder was published in late April 2020,[5] after U.K. pediatricians alerted the National Health Service to an unusual inflammatory illness, termed "pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)," or PIMS-TS.[6] Similar cases were rapidly reported from many other countries.[3,4] The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) subsequently published their own differing definitions of the disorder, which they named multisystem inflammatory syndrome in children (MIS-C).

Two reports now appearing in the *Journal* describe the epidemiology and clinical features of the new disorder in the United States. Dufort and colleagues describe the results of active mandatory surveillance for MIS-C in 106 hospitals in New York State, with 191 cases reported to the state health department as of May 10, 2020, of which 99 met the case definition.[7] Feldstein and colleagues report 186 cases identified by targeted surveillance in 26 U.S. states over a 2-month period.[8] Together with the reports from other countries,[1-6] these studies describe the new childhood inflammatory disorder that has emerged during the Covid-19 pandemic.

With approximately 1000 cases of MIS-C (including, here and below, those that have been classified as PIMS-TS) reported worldwide, do we now have a clear picture of the new disorder, or, as in the story of the blind men and the elephant, has only part of the beast been described? What are its cause and pathogenesis? How should it be diagnosed and treated, and are there wider implications for our understanding of Covid-19?

The published reports have used a variety of hastily developed case definitions based on the most severe cases, possibly missing less serious cases. The CDC and WHO definitions require evidence of SARS-CoV-2 infection or exposure — a requirement that is problematic, since asymptomatic infections are common and antibody testing is neither universally available nor reliable.

Overall, a consistent clinical picture is emerging. MIS-C occurs 2 to 4 weeks after infection with SARS-CoV-2. The disorder is uncommon (2 in 100,000 persons <21 years of age) as compared with SARS-CoV-2 infection diagnosed in persons younger than 21 years of age over the same period (322 in 100,000).[7] Most patients with MIS-C have antibodies against SARS-CoV-2, and virus is detected in a smaller proportion. A

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relatively high proportion of cases have occurred among black, Hispanic, or South Asian persons.[5-8]

Critical illness leading to intensive care develops in some patients, with prominent cardiac involvement and coronary-artery aneurysms in 10 to 20%. Elevated levels of troponin and B-type natriuretic peptide are common in severely affected patients, particularly those with cardiac dysfunction, and most have elevations in levels of C-reactive protein, ferritin, lactate dehydrogenase, and D-dimers, as well as in neutrophil counts. Anemia, lymphopenia, hypoalbuminemia, and abnormal coagulation indexes are also common. Most patients have recovered with intensive care support and after treatment with a range of immunomodulatory agents (including intravenous immune globulin, glucocorticoids, anti–tumor necrosis factor, and interleukin-1 or 6 inhibitors). A small percentage of patients have received extracorporeal membrane oxygenation support, and 2 to 4% have died.

Direct comparison of the clinical and laboratory features of MIS-C with those of Kawasaki's disease suggests that the new disorder is distinct from the latter. Patients with MIS-C are older and have more intense inflammation and greater myocardial injury than patients with Kawasaki's disease, and racial and ethnic predominance differs between the conditions.[6]

There is concern that children meeting current diagnostic criteria for MIS-C are the "tip of the iceberg," and a bigger problem may be lurking below the waterline. Children meeting the broader U.K. definition of PIMS-TS[5] have included critically ill patients, patients meeting diagnostic criteria for Kawasaki's disease, and some patients with unexplained fever and inflammation.[6] Coronary-artery aneurysms have occurred in all three groups.[6] In the study by Dufort et al., one third of the reported patients did not meet their case definition but had clinical and laboratory features similar to those who did.

Clinicians face difficult management issues as they see such a wide spectrum of patients. What treatments may prevent progression to shock and multiorgan failure, and will treatment prevent coronary-artery aneurysms? Are children with self-resolving inflammation at risk for aneurysms, and what cardiac follow-up is needed? Such questions require studies involving not only the patients whose condition meets the current definitions but also children and adolescents who have unexplained fever and inflammation. Indeed, the case definitions may need refinement to capture the wider spectrum of illness. The challenges of this new condition will now be to understand its pathophysiological mechanisms, to develop diagnostics, and to define the best treatment. Most patients to date have been treated with agents that have shown benefit in Kawasaki's disease or other inflammatory disorders; thus, trials are needed to establish the appropriate therapy.

Elucidating the mechanism of this new entity may have importance for understanding Covid-19 far beyond the patients who have had MIS-C to date, who are relatively few in number as compared with those who have had SARS-CoV-2 infection. Because MIS-C generally occurs late after SARS-CoV-2 infection, after antibody has developed, aberrant cellular or humoral adaptive immune responses may be involved. There is evidence that antibodies may enhance the severity of SARS-CoV-1 infection by triggering inflammation or mediating organ damage.[9] Furthermore, genetic studies hint that children carrying variants in genes that regulate T- and B-cell responses or the clearance of immune complexes are at higher risk for Kawasaki's disease.[10] One might speculate that the clinical similarity between Kawasaki's disease and MIS-C implies a related underlying genetic architecture, supporting the hypothesis that the new disorder arises from aberrant T- or B-cell responses to SARS-CoV-2. Given such hypotheses, might an understanding of MIS-C illuminate the elusive pathogenesis of Kawasaki's disease? Furthermore, would it have implications for the development of a safe vaccine against SARS-CoV-2, and could it provide an understanding of the late hyperinflammatory syndrome that occurs in some adults with Covid-19 and that has features similar to those of MIS-C?

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