SARS-CoV-2–Related Inflammatory Multisystem Syndrome in Children
Different or Shared Etiology and Pathophysiology as Kawasaki Disease?

Brian W. McCrindle, MD, MPH; Cedric Manlhiot, PhD

The pediatric inflammatory multisystem syndrome (PIMS) now described in association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has generated considerable interest, both for its severity and delayed emergence in an age group largely spared the complications of primary infection, but also for its overlapping clinical features with Kawasaki disease (KD), the leading cause of acquired heart disease in children in high-income countries.[1] This has prompted considerable discussion that the 2 conditions could have different or shared etiologic and pathophysiologic pathways.

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The article in this issue of *JAMA* by Whittaker et al[2] carefully described a case series of 58 hospitalized patients with severe presentations of PIMS temporally associated with SARS-CoV-2 (PIMS-TS), and in addition importantly compares the clinical and laboratory features with historical cohorts of patients with KD and with KD shock syndrome. Also in this issue, the Research Letter by Cheung et al[3] described similar clinical characteristics for 17 patients with PIMS, 8 of whom also met criteria for typical KD and 5 for incomplete KD. As illustrated in these reports, the differences between PIMS-TS and KD are just as interesting as the similarities.

Five decades of clues have not elucidated the etiology of KD. A genetic predisposition has already been established, evidenced by a male preponderance, racial predisposition (East Asian individuals), and some increased risk in first-degree relatives of affected individuals and twins.[1,4] This genetic predisposition is partially explained by known susceptibility genes that are associated with the immune system.[5] The epidemiology of KD, with marked variations in incidence between countries,[6] region-specific seasonality,[7] periodic outbreaks, and the existence of spatiotemporal clusters,[8,9] suggests that there is more to the etiology of KD than the genetic component alone. Over the years, associations between the distribution of KD and exposure to infectious agents, pollution levels, local weather conditions, concentration of atmospheric biological particles, and early childhood, habitual, or unfamiliar exposures have been documented and postulated to be implicated in the pathophysiology of KD or even to be the etiologic trigger.[9-12] Conflicting studies have been published for almost all of these associations. Some factors have been shown to apply only at a local level; some are associated with the global distribution of case, but none have been shown to have a direct causal relationship with KD.

One of the most common and consistently reported factors associated with KD are infectious diseases. In addition to epidemiological associations, the involvement of infectious disease in the etiology of KD is based on the clinical observation that both infectious disease symptoms and culture-proven infections are common in KD, and specific organisms have been described with some clusters of KD. Many infectious organisms have been suggested as the primary etiology, ranging from toxin-producing *Streptococcus* and *Staphylococcus* to *Mycoplasma* species to a large number of viruses, including coronavirus strains NL63 (2006)[13] and 229E (2014),[14] but the associations have been inconsistent or not replicated.[15,16]

Additional clues as to the etiology of KD have come from pathology studies of fatal cases, which have shown the presence of intracytoplasmic inclusion bodies in bronchial epithelium, analyses of which have suggested the possibility of a novel virus.[17] The normal flora may be involved, particularly that of the gastrointestinal tract. Gastrointestinal infections may be involved as either the trigger or altering susceptibility to the trigger. Animal models have used intraperitoneal injection of *Candida* albicans or *Lactobacillus* casei wall extract to induce a KD-like syndrome in mice. Decades of immunologic studies have suggested that KD is associated with a response to a classic antigen, with activation of the innate immune system, but also features of an adaptive immune response.[1] The trigger and the etiologic and pathophysiologic pathways remain complex and elusive.

Based on a series of studies documenting the epidemiological distribution of KD in Canada,[18] including the examination of spatiotemporal clusters,[8] and a case-control environmental epidemiology study,[19] Manlhiot et al proposed a comprehensive framework for the time and space distribution of KD. The framework ties together many clues as to the etiology and pathogenesis of the disease and addresses the numerous and apparently disjointed epidemiological associations that have been documented with KD over the years. This framework, which has recently been updated, includes 3 major components: a genetic predisposition to KD, immunomodulation through both habitual exposures and environmental factors, and contact with the disease trigger or triggers. In this framework, exposure to the still unidentified trigger(s) results in the development of KD in a genetically susceptible child, with at least a partial contribution from immune-modulating factors. These factors include those that reduce the risk of KD, such as a more abundant habitual exposure to environmental allergens, and those that increase risk, such as pollution. Multiple factors may act sequentially or simultaneously as predisposing, immune-modulating, or triggering agents, altering both individual risk as well as the

incidence of KD in the population across countries or regions. Potential factors found to be associated with KD, either identified through epidemiological association studies or clinical observations, can be integrated into this framework.

PIMS, which has emerged with the SARS-CoV-2 pandemic, shares multiple clinical and laboratory features with KD, such that a substantial proportion of patients included in early reports of PIMS-TS[20,21] also met the American Heart Association criteria for KD.[1] Whittaker et al[2] reported that 7 of the 58 children met criteria for KD and an additional 6 met criteria if coronary artery aneurysm was included. However, it also is clear that PIMS-TS and KD have substantial differences as well as similarities, as the report by Whittaker et al suggests, with age being a major difference (median age, 9 years for children with PIMS-TS vs 2.7 years for those with KD).[2] These observations lead to some speculation, most importantly, the extent to which the etiology and pathophysiology of KD and PIMS-TS might overlap or share commonalities.

These early observations about the characteristics of patients with MIS have already provided some clues. While both conditions have a similar male preponderance, case series suggest that MIS in children may have a different racial/ethnic predilection, affecting primarily people of African American, Caribbean, and Hispanic ancestry, whereas KD affects primarily those of East Asian ancestry. Does this indicate that PIMS-TS might be mediated by a different set of susceptibility genes, or is this related to other factors that are associated with race/ethnicity, including environment and social factors? PIMS-TS also appears to affect an older age group than KD and has a higher prevalence of gastrointestinal symptoms and lower prevalence of classic KD clinical signs. These differences could be associated with 1 or more factors influencing immunomodulation and susceptibility. These observations suggest some areas where suscep-

tibility and immune-modulating factors for PIMS-TS and KD may contribute differently for each condition.

Another important question is whether SARS-CoV-2 directly triggers MIS in children (or perhaps KD), or is it an intermediate primer or co-stimulatory agent or does coronavirus disease 2019 (COVID-19) provide a portal of entry or exposure for the actual trigger? Both a gastrointestinal and respiratory portal of entry, possibly related to infection, have been proposed for KD, and PIMS-TS has affected both systems. The absence of preceding symptoms of COVID-19, often negative polymerase chain reaction result but sometimes positive antibodies or familial exposure, and development of PIMS-TS after a 3- to 6-week lag suggest that SARS-CoV-2 may be acting either as the trigger or an immune-modulating factor. The response to the SARS-CoV-2 pandemic, such as quarantine and social isolation, may have affected children's level of exposure to environmental factors and infections, providing further immune modulation. There has never been a global outbreak of KD where it might be traced to a specific trigger, but this may now be the case. It might be that this is what a specific, unique, and ubiquitous form of KD looks like, providing an important opportunity for investigations to determine factors associated with variations.

With so many questions, how will clinicians and researchers find answers? Careful determination of the unique features of SARS-CoV-2 and the epidemiology, clinical features, genetic and immunologic susceptibility, and pathophysiologic pathways of both PIMS-TS and KD may help to inform the etiologic and pathophysiologic framework for both conditions. The article by Whittaker et al[2] and Research Letter by Cheung et al[3] mark the beginning of an important time of focused discovery, which will likely have relevance to an entire host of inflammatory conditions.

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