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Viewpoint In-Press Preview

Several important features of Multisystem Inflammatory Syndrome in Children (MIS-C) differentiate it from Kawasaki disease. Rowley et al. discuss what is known about MIS-C and the need to elucidate the specific immune mechanisms underlying hyperinflammatory syndromes caused by SARS-CoV-2 to advance potential targeted treatments and prevention efforts.

Immune Pathogenesis of COVID-19-related Multi System Inflammatory Syndrome in Children (MIS-C)

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A.H.R. and S.T.S. are named investigators on Provisional Patent 62/811,930 on Antibodies and Antigens of Kawasaki disease.

An emerging understanding of MIS-C

When cases of SARS-CoV-2-Associated Multisystem Inflammatory Syndrome in Children (MIS-C) were initially reported from Europe, the predominant clinical findings were persistent fever, marked abdominal symptoms, cytokine storm, myocardial dysfunction, and cardiogenic shock with left ventricular dysfunction in the setting of multisystem inflammation, reminiscent of toxic shock syndrome (TSS) or Kawasaki disease shock syndrome (KDSS) and requiring ICU care (1). Other clinical findings included those commonly observed in children with a variety of different infections and non-infectious illnesses, such as conjunctival injection, oral mucosal changes, and rash, features that are overlapping with toxic shock syndrome and incomplete Kawasaki disease. Because mucocutaneous findings are present in children with Kawasaki disease, and because children with MIS-C sometimes developed mild coronary artery dilation, diagnostic confusion initially led some clinicians to conclude that the two conditions were the same (2).

Distinctions from Kawasaki disease

There are several important features of MIS-C that differentiate it from Kawasaki disease (3). Recent data indicate that coronary artery dilation in children with MIS-C is mild and transient (4), similar to that observed in some other febrile illnesses of childhood, including systemic onset juvenile idiopathic arthritis (5). No coronary artery inflammation or necrotizing arteritis has been observed in autopsy studies in adults with COVID-19 (6, 7), and although data on MIS-C patients is limited, a recent case report of an 11-year-old patient described myocarditis in the absence of coronary artery inflammation (8).

It is too early to define the pathological mechanism of coronary artery dilation seen in children MIS-C with certainty, but a likely contributor is the endothelial dysfunction (without morphological changes) associated with SARS-CoV-2 infection, which is sustained by the cytokine storm. This proposed mechanism may explain the less severe and more transient coronary artery dilation in MIS-C patients compared to those with Kawasaki disease. The transient nature of coronary artery findings in MIS-C are in marked contrast to the more severe dilation and coronary artery aneurysm formation observed in Kawasaki disease, which can lead to myocardial infarction, aneurysm rupture, and sudden death (9).

Another important difference between the diseases is in the epidemiology; the highest attack rate and most severe sequelae of Kawasaki disease occur in infants (10-12), whereas the median age of MIS-C appears to be ~9 years of age, with infants relatively spared (13). Moreover, children of Asian descent experience the highest attack rates of Kawasaki disease in the world (10), but no cases of MIS-C have been reported from Asia (14, 15). Finally, marked lymphopenia is a common laboratory finding in MIS-C (13), but is not a feature of Kawasaki disease. A recent study by Carter *et al.*, reported immunophenotyping of MIS-C patients from the UK and concluded that MIS-C presents as an immunopathogenic illness that is distinct from Kawasaki Disease (16).

Classification of MIS-C

Recently, the CDC published initial findings of 570 U.S. children reported to fit their quite broad case definition of MIS-C. The study divided patients into three groups based on latent class analysis, a statistical modeling technique that divides cases into groups

by underlying similarities. Patients in Class 1, which had the highest degree of organ involvement and higher prevalence of shock and lymphopenia, were judged to have little overlap with Kawasaki disease patients. In contrast, patients in Class 3 more commonly met the criteria for Kawasaki disease (13). Patients in Class 2 had the most respiratory symptoms and highest prevalence of nasopharyngeal RT-PCR positivity for SARS-CoV-2, and likely had acute COVID-19. It should be remembered that acute COVID-19 can affect multiple organ systems, and that the presence of multiple organ involvement does not necessarily indicate a diagnosis of MIS-C (17). Some distinctive features of the three classes and Kawasaki disease are listed in Table 1. Based on this analysis, we conclude that Class 1 cases represent “true” MIS-C, and that many children with acute respiratory COVID-19 and with Kawasaki disease, two conditions that are distinct from MIS-C, were unintentionally included among reported cases because the CDC criteria are overly broad.

Need for MIS-C pathogenesis studies

The pathogenesis of MIS-C is unknown, and a post-infectious etiology has been hypothesized but not proven. SARS-CoV-2 antibodies arise in the second week after infection, but their presence does not indicate resolution of infection. A recent study reported inefficient and reduced neutralizing antibody activity against SARS-CoV-2 in children with MIS-C, compared to both adults with severe COVID-19 causing acute respiratory distress syndrome (ARDS), and those who recovered from mild disease, suggesting a reduced protective serological response (18). The virus is generally not

detected in the respiratory tract of children with MIS-C (19), but other compartments such as the gastrointestinal tract have not yet been investigated.

Although the presence of SARS-CoV-2-specific T cells in the peripheral blood of recovered and COVID-ARDS adult patients has been recently been reported (20), no such reports exist among children yet, and the biological significance of SARS-CoV-2-reactive T cells, whether protective or even detrimental, is still unclear (20). A direct effect of SARS-CoV-2 Spike protein structure on immune activation has also been proposed (21). Indeed, recent data suggests that the SARS-CoV-2 Spike protein has a superantigen-like motif with sequence and structure homology to Staphylococcal enterotoxin B (SEB), which could mediate the hyperinflammation observed in MIS-C and in adults with severe COVID19 and cytokine storm (21).

The importance of distinguishing MIS-C and Kawasaki disease

The etiology of Kawasaki disease remains unknown. Although the literature is rife with small unconfirmed studies purporting many different viruses are associated with Kawasaki disease, these appear to be co-incidental and not causative. Indeed, a recent study using the very sensitive VirScan method, covering the complete reference protein sequences of known human viruses, failed to identify evidence of any recent viral infection that was more prevalent in children with Kawasaki disease than febrile childhood controls, including any coronavirus infection (22). A recent study from South Korea reported no temporal association of human coronavirus infection and incidence of Kawasaki disease at the national level (23). Recent research progress supports a presently-unidentified “new” respiratory RNA virus as the cause of the disease (24).

Some have suggested that MIS-C and KD cases should be included together in studies of pathogenesis of the two disorders (25). We take an alternate view. A variety of diverse infectious agents and non-infectious illnesses can cause inflammation affecting multiple organ systems. Although there are some basic commonalities in the immune response to diverse pathogens, the differences outnumber the similarities.

Combining diseases of clearly different etiologies together in studies of the pathogenesis will complicate efforts to understand the true spectrum of MIS-C and to identify its mechanisms and the optimal therapeutic targets. The argument that Kawasaki disease and MIS-C are similar because males are most often affected by both diseases fails to recognize the well-known increased prevalence and severity of most pediatric infectious diseases among males (26). Similarly, the view that MIS-C and KD are part of a spectrum of the same disease because they both respond very well to IVIG and steroids fails to recognize that several diseases with completely separate etiologies and different immunopathologies also respond to nonspecific anti-inflammatory agents such as IVIG and steroids, including several autoimmune and rheumatologic diseases as well as toxic shock syndrome.

As noted in the CDC report, spread of the COVID-19 pandemic may increase the likelihood of patients with Kawasaki disease being misidentified as having MIS-C due to incidental findings of SARS-CoV-2 antibodies (13). Thus, we encourage careful distinction of cases of MIS-C—defined by prolonged fever, severe myocardial dysfunction, severe gastrointestinal symptoms, and lymphopenia with evidence of recent SARS-CoV-2 infection—from those in the differential diagnosis, including Kawasaki disease, prior to initiating any research investigations. This distinction is necessary to

prevent incorrect conclusions being drawn due to the inclusion of unrelated diseases in the same research dataset.

Conclusions

Elucidating the immune mechanisms of hyperinflammatory syndromes caused by SARS-CoV-2 infection, including MIS-C, will provide further insights for more targeted treatment and potentially global prevention efforts. Finally, we believe that ongoing intense basic science investigations into the SARS-CoV-2 viral structures and the host immune response that may lead to the hyperinflammatory syndromes in both children (MIS-C) and adults with severe COVID19 infection (cytokine storm) may provide additional clues to reveal the pathogenesis of these syndromes in the near future.

Table 1. Features of three nonoverlapping groups of children (Class 1, 2, and 3) reported to CDC as MIS-C and comparison with Kawasaki disease

	Class 1 (classic MIS-C)*	Class 2 (acute COVID-19)*	Class 3 (Other conditions including Kawasaki disease)*	Kawasaki disease#
Median age in yrs	9	10	6	1.6
SARS-CoV-2 PCR+, antibody -	0.5%	84%	2%	NA
Abdominal pain	80%	49%	54%	Infrequent
Shock	76%	28%	0%	Rare
Acute respiratory distress syndrome	7%	10%	1.5%	Very rare

*ref 13, #ref 11, NA=not applicable

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