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EDITORIAL COMMENTARY

Diagnosing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Related Multisystem Inflammatory Syndrome in Children (MIS-C): Focus on the Gastrointestinal Tract and the Myocardium

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In this issue of *Clinical Infectious Diseases*, investigators from Spain describe their experience with multisystem inflammatory syndrome in children (MIS-C) during a 3-month period of high prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in their country (Moraleda C et al, in this issue) [1]. Similar to other reports from Europe and the United States [2–5], the vast majority of children with this disorder were in a relatively older age group (median 7.6 years with interquartile range 4.5–11.5 years) and had detectable immunoglobulin G (IgG) antibody to the virus. A minority had viral RNA identified by respiratory reverse transcription polymerase chain reaction (RT-PCR) assay, and respiratory symptoms were uncommon. As reported previously, the classic features of the condition were fever with marked abdominal pain, with or without hypotension and myocardial dysfunction, raising the question as to whether the gastrointestinal tract is the primary site of viral infection in these children [6]. Stool RT-PCR assays were not performed, likely because of a lack of a clinically available, validated viral RT-PCR assay for stool. Whether MIS-C represents cytokine storm resulting from persistent infection of the gastrointestinal tract with SARS-CoV-2, or whether it represents a postinfectious albeit generally short-lived [5, 7, 8] sequelae of viral infection remains unknown.

Children with MIS-C can have findings that are observed in many other infectious and inflammatory illnesses of childhood, such as rash, conjunctival injection, and erythema of the oropharynx. Because these findings are nonspecific, they are not particularly helpful in establishing the diagnosis. Because these features are present in patients with Kawasaki disease (KD), some clinicians view MIS-C and KD as the same clinical entity [1, 9]. But does it make sense to consider these to be the same disorder? The epidemiology of KD has remained consistent and unchanged worldwide for >50 years, with the vast majority of cases occurring in children ≤5 years of age. Asian children are at highest risk [10, 11]. Because there is presently no diagnostic test for KD, an essential component of the diagnosis is exclusion of illnesses with similar clinical features, as stated in the American Heart Association Guideline on Kawasaki Disease Diagnosis, Treatment, and Long-Term Management, "because the principal clinical findings that fulfill the diagnostic criteria are not specific" [12]. As noted by Moraleda and colleagues, it is now clear that MIS-C is related to SARS-CoV-2 infection, and the fact that this virus is entirely new to the human population indicates that it cannot be responsible for an illness that was well established for decades prior to its emergence. Moreover, the presence of virus-like intracytoplasmic inclusion bodies in KD tissues that are targeted by antibodies produced by patients following the disease strongly suggests a single presently unidentified viral agent or closely related group of viruses as the cause [13–15], rather than multiple disparate etiologic agents. In marked contrast to KD, MIS-C has consistently been observed to target older children and adolescents [3, 16], and the condition has not been observed in Asia [17, 18]. KD can result in potentially severe coronary artery complications, which require long-term monitoring, treatment, and follow-up [12]. It has been consistently reported that MIS-C can result in coronary artery dilation [3, 5], which could potentially be due to interleukin 6 cytokine storm similar to that observed in systemic onset juvenile rheumatoid arthritis [19]. Persisting

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aneurysms from MIS-C have not yet been reported. Given the broad case definition of MIS-C, which includes KD clinical features, children who are diagnosed with MIS-C and develop persisting aneurysms may actually have had KD. This is particularly true for infants, such as the 6-month-old infant described by Moraleda and colleagues, because infants appear to rarely develop MIS-C. In a recent study of 186 cases of MIS-C in the United States, there were no patients under 1 year of age with IgG antibody to SARS-CoV-2 in the cohort [3]. This is in striking contrast to the high attack rate and high risk of severe coronary artery aneurysms in infants with KD [10, 20, 21]. In areas with a high prevalence of SARS-CoV-2 infection, children with KD could have evidence of concurrent unrelated SARS-CoV-2 infection and be misclassified as MIS-C, as acknowledged by Moraleda and colleagues. Indeed, the authors noted that more than one-fourth of the positive screening tests for the virus in children in Spain during the time period of their report were in children with asymptomatic SARS-CoV-2 infection admitted for an unrelated medical problem.

The very broad case definition for MIS-C is of concern when performing urgently needed research studies to understand the pathogenesis and long-term sequelae of this condition, because inclusion of children who have other conditions will skew results and obscure accurate conclusions. The unique clinical features of MIS-C appear to be those related to the gastrointestinal tract and the myocardium. It is presently unknown whether myocardial dysfunction in MIS-C results from myocardial inflammation or myocardial edema related to cytokine storm, but the latter seems more likely, in view of the relatively rapid improvement in most children [5]. Similarly, the mechanism of gastrointestinal involvement is also unclear. When exploratory abdominal surgery has been performed in cases of MIS-C, the findings have been diffuse inflammation of the intestine and/or mesenteric lymphadenitis [5, 7]. Research studies of MIS-C should focus initially on older children and adolescents with the classic presentation of fever with severe abdominal pain, hypotension, and myocardial dysfunction, to avoid inclusion of children with KD and KD shock, acute coronavirus disease 2019 (COVID-19), other viral infections, and other conditions that fulfill the current MIS-C case definition. Because SARS-CoV-2 cases are increasing in the United States, particularly in Southern and Western states, cases of MIS-C will unfortunately continue to be observed. Fortunately, MIS-C remains uncommon, and children appear to improve rapidly with intravenous gammaglobulin and/or corticosteroid therapy. Hopefully, vaccine development will soon be successful, to enable prevention of COVID-19 respiratory disease, MIS-C, and other complications of SARS-CoV-2 infection.

Note

Potential conflicts of interest. A. H. R. reports patent 62/811 930 pending for antigens and antibodies of Kawasaki disease; National Institutes of Health (NIH) support for identifying antigens and antibodies of Kawasaki disease, and a grant from the Falk Medical Catalyst Award for identifying a viral etiology of Kawasaki disease, outside the submitted work. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Moraleda C, Serna-Pascual M, Soriano-Arandes A, et al. Multi-inflammatory syndrome in children related to SARS-CoV-2 in Spain. Clin Infect Dis **2020**.
2. Dufort EM, Koumans EH, Chow EJ, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. N Engl J Med **2020**; 383:347–58.
3. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med **2020**; 383:334–46.
4. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA **2020**.
5. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation **2020**.
6. Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science **2020**; 369:50–4.
7. Cabrero-Hernández M, García-Salido A, Leoz-Gordillo I, et al. Severe SARS-CoV-2 infection in children with suspected acute abdomen: a case series from a tertiary hospital in Spain. Pediatr Infect Dis J **2020**; 39:e195–8.
8. Kaushik S, Aydin SI, Derespina KR, et al. Multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection: a multi-institutional study from New York City. J Pediatr **2020**.
9. Ouldali N, Pouletty M, Mariani P, et al. Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: a time-series analysis. Lancet Child Adolesc Health **2020**.
10. Makino N, Nakamura Y, Yashiro M, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015–2016. Pediatr Int **2019**; 61:397–403.
11. Holman RC, Christensen KY, Belay ED, et al. Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. Hawaii Med J **2010**; 69:194–7.
12. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation **2017**; 135:e927–99.
13. Rowley AH, Baker SC, Arrollo D, et al. A protein epitope targeted by the antibody response to Kawasaki disease. J Infect Dis **2020**; 222:158–68.
14. Rowley AH, Baker SC, Shulman ST, et al. Cytoplasmic inclusion bodies are detected by synthetic antibody in ciliated bronchial epithelium during acute Kawasaki disease. J Infect Dis **2005**; 192:1757–66.
15. Rowley AH, Baker SC, Shulman ST, et al. Ultrastructural, immunofluorescence, and RNA evidence support the hypothesis of a "new" virus associated with Kawasaki disease. J Infect Dis **2011**; 203:1021–30.
16. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet **2020**; 395:1607–8.
17. Kim YJ, Park H, Choi YY, et al. Defining association between COVID-19 and the multisystem inflammatory syndrome in children through the pandemic. J Korean Med Sci **2020**; 35:e204.
18. Xu S, Chen M, Weng J. COVID-19 and Kawasaki disease in children. Pharmacol Res **2020**; 159:104951.
19. Binstadt BA, Levine JC, Nigrovic PA, et al. Coronary artery dilation among patients presenting with systemic-onset juvenile idiopathic arthritis. Pediatrics **2005**; 116:e89–93.
20. Cameron SA, Carr M, Pahl E, DeMarais N, Shulman ST, Rowley AH. Coronary artery aneurysms are more severe in infants than in older children with Kawasaki disease. Arch Dis Child **2019**; 104:451–5.
21. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics **2003**; 112:495–501.