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CHEST

Multisystem Inflammatory Syndrome in Adults

Coming Into Focus

Mark W. Tenforde, MD, PhD
Sapna Bamrah Morris, MD
Atlanta, GA

Multisystem inflammatory syndrome in children (MIS-C) has become a recognized syndrome, whereas a parallel syndrome in adults has not been well defined. MIS-C was first reported in April 2020 as a hyperinflammatory syndrome with variable features of Kawasaki disease.[1] Most cases occur several weeks following confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children or young adults (< 21 years of age) who develop severe illness. The syndrome is characterized by fever, markedly elevated inflammatory biomarkers, and multiple organ system involvement, frequently with prominent GI symptoms.[1,2] Shock and cardiac injury are common, and typical features include elevated cardiac biomarkers, left ventricular dysfunction, coronary dilatation, and requirement for vasopressor or inotrope support. The pathophysiology of cardiac dysfunction as among the most severe manifestations was not characterized in initial case series of MIS-C,[1,2] and several potential mechanisms of cardiac injury are plausible.[3-7] Features of MIS-C, including an older age distribution and race/ethnicity of cases with infrequent occurrence in children of Asian descent, distinguish it from Kawasaki disease and suggest greater population susceptibility, including in adults.[2,8] Cases in children have likely been evident because of the dramatic clinical illness that is usually observed in previously healthy children, most of whom were not expected to develop severe coronavirus disease 2019 (COVID-19). Although it may be initially obscured by severe COVID-19 illness in adults with cardiac or other co-morbidities, the evidence for multisystem inflammatory syndrome in adults (MIS-A) has expanded.

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AFFILIATIONS: From the CDC COVID-19 Response Team, Centers for Disease Control and Prevention.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

CORRESPONDENCE TO: Sapna Bamrah Morris, MD, 1600 Clifton Rd NE, MS US12-4, Atlanta, GA 30329; e-mail: feu3@cdc.gov

DOI: https://doi.org/10.1016/j.chest.2020.09.097

In this issue of *CHEST*, Hékimian et al[9] describe 11 generally healthy patients aged 16 to 40 years (seven people aged > 18 years) who presented with clinical and laboratory characteristics of MIS with cardiac dysfunction requiring intensive care support that included vasopressors and inotropes. The presence of SARS-CoV-2 antibodies, which develop within about 2 weeks of infection in most patients with SARS-CoV-2 infection,[10] coupled with negative real-time reverse transcriptase polymerase chain reaction (RT-PCR), which is used to identify acute COVID-19, suggested that SARS-CoV-2 infection had occurred in a majority of cases several weeks prior, followed by a postinfectious inflammatory syndrome. The authors describe radiographic evidence of edematous myocarditis on cardiac MRI in all six patients who underwent imaging. However, further research is needed to understand the pathophysiology of cardiac injury, including cellular and molecular mechanisms.

Following infection, adults with acute COVID-19 often experience fever accompanied by respiratory symptoms (eg, cough, shortness of breath). A minority of patients experience persistent and worsening symptoms, usually dyspnea, compelling them to seek health-care attention. A small proportion of patients progress to a later stage of COVID-19, at times referred to as the cytokine storm. This late stage can include coagulopathy and multiorgan dysfunction in the setting of severe inflammation. In contrast, the patients presented by Hékimian et al[9] sought care after having fever, abdominal pain, nausea, vomiting, varied mucocutaneous findings, and often symptoms indicative of myocardial dysfunction accompanied by severe inflammation.

This report[9] is an important addition to descriptions of MIS-A.[4,6,7,11-13] Other published case reports and case series of suspected MIS-A have described case presentations similar to those reported by Hékimian

et al.[9] Markedly elevated laboratory markers of coagulopathy and inflammation and evidence of cardiac dysfunction are typical, and can also be observed in severe acute COVID-19. Although the clinical presentation in some patients with severe COVID-19 could overlap with MIS-A, the pathophysiology may be different; distinguishing between the two syndromes has implications for treatment and long-term follow-up. For example, Hékimian et al identified patients who were not on a continuum of severe COVID-19 but rather developed severe nonpulmonary manifestations without the typical features of a primary viral pneumonia. Dual SARS-CoV-2 RT-PCR and antibody testing, and a thorough history focusing on whether the patient had preceding epidemiologic links to COVID-19 cases or previous (sometimes subtle) symptoms of COVID-19, can provide supportive evidence for suspected MIS-A. Findings of a negative RT-PCR test result and positive antibody test result in the setting of a suggestive clinical history and presentation may be helpful. However, issues with tests include that RT-PCR may stay positive for several weeks, antibody assays have imperfect sensitivity, and patients may have had remote previous exposure to SARS-CoV-2 with persistent antibody positivity.

Several features of MIS-A require urgent attention. First, a lack of clear guidance regarding diagnosis highlights the need to establish MIS-A case definitions and testing algorithms. Although antibody testing is strongly recommended by the Infectious Diseases Society of America in the setting of MIS-C,[14] the role of antibody testing for cases of suspected MIS-A needs to be defined. Second, optimal treatment is unclear at this time and will likely require evidence outside of randomized controlled trials given the rarity of this syndrome. IV immunoglobulin, steroids, and other immunomodulatory agents have been used to treat suspected cases of MIS-A, with clinical improvement noted in some instances. Third, the potential for chronic sequelae in affected patients is not yet known and could affect long-term follow-up care and monitoring, such as repeat echocardiography. Finally, further studies on the immunopathogenesis of this syndrome are needed. If MIS is postinfectious or antibody mediated, there could be important implications for vaccine safety.

Although recognition of MIS-C is now widespread among pediatric providers, MIS-A is gaining recognition among providers caring for adults. MIS-A is likely a rare but important syndrome that can be difficult to distinguish from severe COVID-19, particularly in older patients with multiple comorbidities. Hékimian et al[9] present compelling evidence for MIS-A, specifically in young adults, and prepare providers with further awareness and insights into this emerging syndrome.

Acknowledgments

Other contributions: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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