

Received: 2021.10.03
Accepted: 2021.10.04
Available online: 2021.10.06
Published: 2021.10.11

Editorial: Multisystem Inflammatory Syndrome in Adults (MIS-A) and the Spectrum of COVID-19

Dinah V. Parums, MD PhD

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

e-mail: dinah.v.parums@isi-science.com

Conflict of interest: None declared

Abstract

Recent studies on the pathogenesis and clinical spectrum of human disease following infection with the new human pathogen, SARS-CoV-2, have identified the varied presentations and sequelae of COVID-19. Acute 'cytokine storm' in severe COVID-19 results in multiorgan damage due to vascular hyperpermeability, edema, and hypercoagulation. The long-term consequences of infection from SARS-CoV-2 include long COVID, or post-COVID syndrome, and multisystem inflammatory syndrome in children (MIS-C). Several case reports of multisystem inflammatory syndrome in adults (MIS-A) have shown the presentation at more than four weeks after initial infection with SARS-CoV-2 in adults more than 21 years of age. In September 2021, a published systematic review of the literature identified 221 patients with MIS-A, representing the most comprehensive clinical study to date. MIS-A occurs in the post-acute COVID-19 period. The pathogenesis may involve a dysregulated antibody-mediated immune response, similar to MIS-C. Therefore, patients with MIS-A may respond to supportive therapies that control hyperinflammation. This Editorial aims to describe MIS-A and discuss COVID-19 as a spectrum of hyperinflammatory disease in terms of severity, extent, duration, and patient age.

Keywords: **Multisystem Inflammatory Disease, Adults, MIS-A • SARS-CoV-2 • COVID-19 • Editorial**

Recent studies on the pathogenesis and clinical spectrum of human disease following infection with the new human pathogen, SARS-CoV-2, have begun to identify and define the varied presentations and sequelae of COVID-19 [1,2]. Understanding the mechanisms of diseases such as COVID-19 is the basis for diagnosis and prevention [1,2]. Ongoing studies based on current knowledge of the pathogenesis of COVID-19 underpin the development of new approaches to treatment, including antiviral agents and anti-inflammatory agents [3,4]. Some patients with COVID-19 are asymptomatic, some have a moderate or severe respiratory illness, and some require hospitalization and ventilatory support [5]. The classification of disease severity and the risk factors for developing severe COVID-19 have been studied to identify clinical risk factors for disease severity, hospitalization, and mortality [5,6]. However, there is a range of systemic and organ-specific inflammatory events associated with SARS-CoV-2 infection in different age groups and at different stages of infection that remains, as yet, both enigmatic and unpredictable [7,8].

Patients with severe acute COVID-19 pneumonia may develop 'cytokine storm,' or activation of the innate immune response, including inflammatory signaling pathways and cytokines [8]. The 'cytokine storm' results in acute respiratory distress syndrome (ARDS) and is also associated with the downregulation of angiotensin-converting enzyme 2 (ACE2), which results in

dysfunction of the renin-angiotensin system (RAS) [8]. The acute 'cytokine storm' that occurs in patients with severe COVID-19 results in multiorgan damage due to vascular hyperpermeability, edema, and hypercoagulation [8,9].

The long-term consequences of infection from SARS-CoV-2 include long COVID, or post-COVID syndrome, and multisystem inflammatory syndrome in children (MIS-C) [10,11]. Long COVID occurs in between 10% and 30% of adult patients who recover from initial acute infection with SARS-CoV-2 [10]. Long COVID includes pulmonary, hematologic, cardiovascular, renal, neuropsychiatric, renal, hepatobiliary, gastrointestinal, and dermatologic clinical complications [10]. MIS-C was first identified in April 2020 and is also a form of long COVID in children and adolescents [11]. The US Centers for Disease Control and Surveillance (CDC) criteria for the diagnosis of MIS-C include age <21 years and a clinical presentation requiring hospitalization, and positive laboratory for current or recent SARS-CoV-2 infection, or SARS-CoV-2 exposure, within the past four weeks [11]. Both long COVID in adults and MIS-C in children may be due to the systemic effects of inflammatory tissue damage [10,11].

Recently, there has been further clinical support that the pathogenesis of COVID-19 involves a spectrum of mild and severe, acute and chronic, respiratory and multisystem inflammatory syndromes that affect all age groups [13-15]. Multisystem

inflammatory syndrome in adults (MIS-A) has recently been described [12-15]. MIS-A presents more than four weeks after initial infection with SARS-CoV-2 in young adults more than 21 years of age [12-15]. Although there have been several case reports of MIS-A in young adults, it was not until August 2021 that Davogustto and colleagues described 15 adult patients with MIS-A who had a recent infection with SARS-CoV-2, confirmed by laboratory testing [13]. This study compared patients with MIS-A with young adult patients presenting with acute COVID-19 [13]. Compared with acute SARS-positive patients with acute COVID-19, patients with MIS-A were younger and had positive SARS-CoV-2 serology, and 33.3% required admission to the intensive care (ICU) [13]. As with cases of MIS-C, none of the cases of MIS-A were fatal [13]. These investigators noted an overlap between the symptoms of acute COVID-19 and MIS-A in 60% of cases studied [13].

Currently, there are several unknowns regarding the diagnosis and pathogenesis of MIS-A. The clinical overlap between MIS-A and acute COVID-19 is likely to make it difficult to diagnose. This diagnostic difficulty is less likely in children who mainly have an asymptomatic infection or mild COVID-19 symptoms before presenting with symptomatic MIS-C [11,13,15]. Also, there may be a diversity of individual and age-related phenotypes for MIS-A [13,15]. Children with MIS-C in younger cohorts more commonly present with mucocutaneous symptoms and signs [11,14]. Children in older cohorts present with gastrointestinal symptoms and myocarditis [11,14].

A systematic review of the literature on reported cases and studies, published in September 2021, represents the most comprehensive clinical information in MIS-A to date [15]. Patel and colleagues reviewed 221 patients with MIS-A from the published literature and cases reported to the US Centers for Disease Control and Prevention (CDC) between May 2020 to May 2021 [15]. The review identified 221 patients with MIS-A worldwide [15]. Patients presented with MIS-A approximately four weeks after an initial diagnosis of acute COVID-19 [15]. The median age of the 221 patients with MIS-A was 21 years (range, 19-34 years), 70% were men, 58% had no underlying comorbidity, and 68% reported a previous symptomatic COVID-19-like illness at a median of 28 days previously [15]. The main presenting symptoms of MIS-A were fever (96%),

hypotension (60%), cardiac dysfunction (54%), shortness of breath (52%), and diarrhea (52%) [15]. This review showed that in patients with MIS-A, the median number of organ systems involved was five, the median hospital stay was 8 days (range, 5-12 days) [15]. Also, 57% of patients were admitted to the ICU, 47% required respiratory support, and 7% of patients with MIS-A died following hospital admission [15]. Most patients with MIS-A (90%) had increased coagulopathy or inflammatory markers, and 72% had a positive serological test for SARS-CoV-2 [15]. The authors concluded that MIS-A with extrapulmonary multiorgan involvement was difficult to discern from both acute biphasic COVID-19 and post-acute sequelae of SARS-CoV-2 infection [15]. The findings from this review supported that MIS-A is a post-acute COVID-19 syndrome with a heterogeneous clinical presentation due to a dysregulated immune response [15,16]. Also, identifying post-acute COVID-19 syndromes, including MIS-C and MIS-A, highlights the importance of accurate serological testing for SARS-CoV antibodies [17].

Currently, there are insufficient studies on patients with MIS-A to identify different clinical presentations of MIS-A with age. Currently, there is no evidence to support the optimal treatment strategy for MIS-A, which is likely to require symptomatic or supportive care. Children with MIS-C are treated with intravenous immunoglobulin (IVIg) and glucocorticoids [11,14]. However, there is no evidence to support whether these treatments will be effective in patients with MIS-A.

Conclusions

There remain many questions regarding the presentation, pathogenesis, and outcome of MIS-A. Until more is known about the clinical presentation of MIS-A and its diagnosis, future cases are likely to be unrecognized. Because cases of MIS-A occur in the post-acute COVID-19 period, the pathogenesis may involve a dysregulated antibody-mediated immune response, similar to MIS-C. Therefore, patients with MIS-A may respond to supportive therapies that control hyperinflammation. Although the incidence of MIS-A is unknown, as with MIS-C in children, MIS-A is likely to be an uncommon complication of SARS-CoV-2 infection in adults.

References:

1. Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. *Postgrad Med J.* 2021;97(1147):312-20
2. Nature News. May 5, 2021. COVID research: a year of scientific milestones. *Nature.* 2021; doi: 10.1038/d41586-020-00502-w. Epub ahead of print. Available from: <https://www.nature.com/articles/d41586-020-00502-w>
3. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for COVID-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980
4. Malone B, Campbell EA. Molnupiravir: Coding for catastrophe. *Nat Struct Mol Biol.* 2021;28(9):706-8
5. Li X, Zhong X, Wang Y, et al. Clinical determinants of the severity of COVID-19: A systematic review and meta-analysis. *PLoS One.* 2021;16(5):e0250602
6. National Institutes of Health (NIH). COVID-19 treatment guidelines. Clinical spectrum of SARS-CoV-2 infection. 2021. Available from: <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>

7. Weatherhead JE, Clark E, Vogel TP, et al. Inflammatory syndromes associated with SARS-CoV-2 infection: dysregulation of the immune response across the age spectrum. *J Clin Invest*. 2020;130(12):6194-97
8. Choudhary S, Sharma K, Silakari O. The interplay between inflammatory pathways and COVID-19: A critical review on pathogenesis and therapeutic options. *Microb Pathog*. 2021;150:104673
9. Webb BJ, Peltan ID, Jensen P, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: A cohort study. *Lancet Rheumatol*. 2020;2(12):e754-63
10. Parums DV. Editorial: Long COVID, or post-COVID syndrome, and the global impact on health care. *Med Sci Monit*. 2021;27:e933446
11. Parums DV. Editorial: COVID-19 and multisystem inflammatory syndrome in children (MIS-C). *Med Sci Monit* 2021;27:e933369
12. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection – United Kingdom and United States, March-August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(40):1450-56
13. Davogusto GE, Clark DE, Hardison E, et al. Characteristics associated with multisystem inflammatory syndrome among adults with SARS-CoV-2 infection. *JAMA Netw Open*. 2021;4(5):e2110323
14. 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(4):347-58
15. Patel P, DeCuir J, Abrams J, et al. Clinical characteristics of multisystem inflammatory syndrome in adults: A systematic review. *JAMA Netw Open*. 2021;4(9):e2126456
16. Chow EJ. The multisystem inflammatory syndrome in adults with SARS-CoV-2 infection – another piece of an expanding puzzle. *JAMA Netw Open* 2021;4(5):e2110344
17. Hanson KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: Serologic testing. *Infectious Diseases Society of America (IDSA)*. Available from: <https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/>