Post–COVID-19 multisystem inflammatory syndrome in children

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Abstract

Question The effect of acute coronavirus disease 2019 (COVID-19) on morbidity and mortality in children has been relatively small. If a child presents to my office with persistent fever and systemic hyperinflammation but no known exposure to COVID-19, how likely are they to have multisystem inflammatory syndrome in children (MIS-C)? What is currently known about MIS-C and what is the prognosis for children affected by it?

Answer Amid the COVID-19 pandemic, the emergence of a novel condition presents yet another challenge to clinicians, public health professionals, and the pediatric population. Multisystem inflammatory syndrome in children is a rare but potentially severe condition seen in children with evidence of COVID-19 approximately 2 to 6 weeks before symptom onset. Common signs and symptoms include persistent fever, systemic hyperinflammation, gastrointestinal symptoms (eg, abdominal pain, vomiting, diarrhea), mucocutaneous changes (eg, rash, conjunctivitis), headache, or cardiac dysfunction. As many children present as asymptomatic or with mild symptoms of COVID-19, the development of MIS-C can seem sudden and surprising to families and providers. Although children with MIS-C usually require hospitalization, the outcomes are largely favourable with prompt recognition and intense therapy.

Since its emergence, the rapid transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known to cause the novel coronavirus disease 2019 (COVID-19), has resulted in high morbidity and mortality worldwide.[1] While the virus affects all age groups, children were thought to fare better during the COVID-19 illness, as this population accounted for only 1% to 5% of those diagnosed with the illness and rarely developed severe disease.[2] Most children with COVID-19 present with a range of signs and symptoms that are not severe or specific enough to prompt disease testing.[3] Some children and adolescents show no symptoms at all.[3] The challenge with unrecognized COVID-19 cases is that asymptomatic children might become silent carriers in the community[3,4] or be at risk of developing post–COVID-19 complications.

One of the rare, yet potentially life-threatening, complications of COVID-19 in children is a condition known as *multisystem inflammatory syndrome in children* (MIS-C),[5] also referred to as *pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2* or *PIMS-TS*. Multisystem inflammatory syndrome in children is a febrile syndrome characterized by systemic hyperinflammation, persistent fever, and multisystem organ dysfunction.[6,7] The first case of MIS-C was reported in the United Kingdom in April 2020.[8] Since then, more than 4000 cases of MIS-C have been confirmed in the United States alone,[9] with evidence suggesting MIS-C is likely a secondary consequence of COVID-19 in children. A concentration of subsequent cases was observed 4 to 6 weeks following the peak of adult COVID-19 cases in the United States and France[5] and 2 to 5 weeks following the peaks of pediatric COVID-19 cases that occurred in early May and August 2020 in the United States.[10] Further, more than 70% of MIS-C patients had seropositive test results for antibodies against SARS-CoV-2.[11,12]

Unknown pathogenesis

While the exact cause is currently unknown, children presenting with MIS-C symptoms demonstrate hyperinflammatory immune response secondary to the SARS-CoV-2 infection.[11] A number of possible theories have been proposed. Yonker et al[13] found significantly (P=.004) elevated levels of SARS-CoV-2 S1 protein in patients with MIS-C compared with healthy controls, and increased (P=.003) levels of zonulin in the blood—a protein that regulates gastrointestinal permeability by modulating intercellular tight junctions. The increased gut permeability, caused by elevated zonulin levels, allows for the leakage of SARS-CoV-2 antigens into the bloodstream.[13] A recent discovery of a superantigenlike motif near the S1/S2 cleavage site on the SARS-CoV-2 spike protein supports this mechanism and has been hypothesized to trigger the MIS-C hyperinflammatory response by interacting with T cell receptors and major histocompatibility complex class II molecules.[14] Additionally, a deep immune profiling of MIS-C patients by Vella et al[15] found an increased activation of $CX3CR1^+$ $CD8^+$ T cells associated with persistent SARS-CoV-2 antigen and vascular surveillance. Further research into the immunology and pathophysiology of MIS-C is crucial to improving the diagnosis and treatment of children affected by this disease, as well as possibly understanding the different severity of acute COVID-19 in children and addressing future vaccination plans.

Recognition and symptoms

Contrary to the low rates of severe symptoms shown with COVID-19, children with MIS-C have presented with

various symptoms from fever to cardiogenic shock.[16] A study of 1733 MIS-C patients in the United States reported that 90.4% of patients had complications involving at least 4 organ systems and 58.2% were admitted for intensive care.[10] Some of the most common signs and symptoms included abdominal pain (66.5%), vomiting (64.3%), rash (55.6%), diarrhea (53.7%), and conjunctival hyperemia (53.6%).[10] A study endorsed by working groups for cardiac imaging and cardiovascular intensive care from the Association for European Paediatric and Congenital Cardiology reported that a cohort of 286 MIS-C patients across 17 European countries had myocardial involvement (93%), gastrointestinal symptoms (71%), shock (40%), and cardiac arrhythmia (35%).[17] All patients presented with persistent fever (>38°C) and had elevated laboratory markers of inflammation such as C-reactive protein, serum ferritin, procalcitonin, IL-6, and D-dimer levels.[17] Most were previously healthy children and adolescents with no comorbidities.[17]

Differentiating MIS-C from other hyperinflammatory diseases, such as Kawasaki disease (KD) and toxic shock syndrome, has been challenging for clinicians. Patients with MIS-C tend to be older than those with KD (mean age 8 to 9 years vs 2 to 3 years, respectively), and present with elevated troponin levels.[5] Prominent symptoms of abdominal pain and cardiac dysfunction might help to distinguish the condition from toxic shock syndrome and KD.[5]

Affecting minorities

Several studies[18–20] from the United States highlight the disproportionate effect of MIS-C among children in Black and Hispanic communities. A retrospective analysis of the US Centers for Disease Control and Prevention MIS-C surveillance database found that the median age of patients with MIS-C was 8 years, 602 of 1080 (56%) patients were male, and 724 of 945 (77%) patients were either Hispanic or non-Hispanic Black.[18] The study also found that intensive care unit admissions and decreased cardiac function were more likely in non-Hispanic Black patients compared with non-Hispanic White patients.[18]

Management

The American College of Rheumatology published clinical guidelines for MIS-C. They included a high level of consensus for administering high-dose intravenous immunoglobulin (IVIG) (2 g/kg based on ideal body weight), glucocorticoids, or both as first-tier agents.[21] For patients with cardiac dysfunction, IVIG may be given as 1 g/kg daily over 2 days and might require close monitoring and diuretics.[21] Methylprednisolone or other steroids may be used as first-line therapy at 1 to 2 mg/kg daily for patients who show highly elevated levels of B-type natriuretic peptides, unexplained tachycardia, or ill appearance, but who have not yet developed shock or organ-threatening conditions.[21] A combination therapy might be favoured, as Ouldali et al[22] found that patients treated with IVIG and methylprednisolone had a more favourable course, lower risk of treatment failure, and shorter duration of stay in the pediatric intensive care unit (4 vs 6 days) than patients who received IVIG alone. Additionally, low-dose acetylsalicylic acid (3 to 5 mg/kg daily up to 81 mg/d) is recommended as part of antiplatelet therapy in MIS-C patients without serious bleeding risk.[21] Targeted neutralization of inflammatory cytokines with IL-1 receptor antagonist (eg, anakinra)[21] or IL-6 receptor antagonist (eg, tocilizumab)[11] has also been found to be effective as second-line therapy. The median hospital stay was 6 days, with generally positive outcomes.[11]

A recently published multidisciplinary retrospective study[23] of 46 adolescents with MIS-C provided insights into outcomes at 6 months' follow-up. At 6 months, systemic inflammation was resolved in 45 patients, echocardiogram findings were normal in 44 patients, and only 6 patients reported gastrointestinal symptoms.[23] Minor neurologic abnormalities were detected in 18 patients but these did not correlate with neurologic functional impairments.[23] Other findings at 6 months included muscular fatigue, anxiety, and emotional lability.[23] Although the long-term consequences will become clearer with further follow-up, prompt recognition results in favourable outcomes for MIS-C.[11]

Conclusion

Multisystem inflammatory syndrome in children has closely followed in the footsteps of the COVID-19 pandemic and has presented itself as a rare, but potentially life-threatening, complication of the disease in children. Prompt recognition of this febrile syndrome and efforts to reduce the risk of exposure to COVID-19 in children and adolescents, especially those from minority or socioeconomically disadvantaged populations, are key to limiting the incidence of MIS-C.

Competing interests
None declared

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References

1. Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med* 2021;9(3):251-9. Epub 2020 Dec 17.
2. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr* 2020;109(6):1088-95. Epub 2020 Apr 14.
3. Han MS, Choi EH, Chang SH, Jin BL, Lee EJ, Kim BN, et al. Clinical characteristics and viral RNA detection in children with coronavirus disease 2019 in the Republic of Korea. *JAMA Pediatr* 2021;175(1):73-80.
4. DeBiasi RL, Delaney M. Symptomatic and asymptomatic viral shedding in pediatric patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): under the surface. *JAMA Pediatr* 2021;175(1):16-8.
5. Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Moceri P, et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2021;39(22):3037-49. Epub 2021 Feb 25.
6. Rubens JH, Akindele NP, Tschudy MM, Sick-Samuels AC. Acute COVID-19 and multisystem inflammatory syndrome in children. *BMJ* 2021;372:n385.
7. Rafferty MS, Burrows H, Joseph JP, Leveille J, Nihtianova S, Amirian ES. Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: current knowledge and implications for public health. *J Infect Public Health* 2021;14(4):484–94. Epub 2021 Jan 18.

8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;395(10237):1607-8. Epub 2020 May 7.
9. *Multisystem inflammatory syndrome in children (MIS-C).* Atlanta, GA: Centers for Disease Control and Prevention; 2020. Available from: **https://www.cdc.gov/mis-c/cases/index.html**. Accessed 2021 Jun 12.
10. Belay ED, Abrams J, Oster ME, Giovanni J, Pierce T, Meng L, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. *JAMA Pediatr* 2021:e210630. Epub ahead of print.
11. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell* 2020;183(4):982-95.e14. Epub 2020 Sep 14.
12. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020;383(4):334-46. Epub 2020 Jun 29.
13. Yonker LM, Gilboa T, Ogata AF, Senussi Y, Lazarovits R, Boribong BP, et al. Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier. *J Clin Invest* 2021:149633. Epub ahead of print.
14. Cheng MH, Zhang S, Porritt RA, Rivas MN, Paschold L, Willscher E, et al. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. *Proc Natl Acad Sci U S A* 2020;117(41):25254-62. Epub 2020 Sep 28.
15. Vella LA, Giles JR, Baxter AE, Oldridge DA, Diorio C, Kuri-Cervantes L, et al. Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. *Sci Immunol* 2021;6(57):eabf7570.
16. Ramaswamy A, Brodsky NN, Sumida TS, Comi M, Asashima H, Hoehn KB, et al. Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. *Immunity* 2021;54(5):1083-95.e7. Epub 2021 Apr 13.
17. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. *Circulation* 2021;143(1):21-32. Epub 2020 Nov 9.
18. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health* 2021;5(5):323-31. Epub 2021 Mar 9.
19. Javalkar K, Robson VK, Gaffney L, Bohling AM, Arya P, Servattalab S, et al. Socioeconomic and racial and/or ethnic disparities in multisystem inflammatory syndrome. *Pediatrics* 2021;147(5):e2020039933. Epub 2021 Feb 18.
20. Lee EH, Kepler KL, Geevarughese A, Paneth-Pollak R, Dorsinville MS, Ngai S, et al. Race/ethnicity among children with COVID-19–associated multisystem inflammatory syndrome. *JAMA Netw Open* 2020;3(11):e2030280. Epub 2020 Nov 30.
21. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. *Arthritis Rheumatol* 2021;73(4):e13-29. Epub 2021 Feb 15.
22. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA* 2021;325(9):855-64.
23. Penner J, Abdel-Mannan O, Grant K, Maillard S, Kucera F, Hassell J, et al. 6-Month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *Lancet Child Adolesc Health* 2021;5(7):473-82. Epub 2021 May 24.

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