REVIEW ARTICLE

Multi-systemic inflammatory syndrome in childhood (MIS-C): A review article

Nabeeha Najatee Akram,[1] Wassan Nori,[2] Khalid Waleed Al Qaissi,[3] Bahaa ALdeen Abdulrahman Hadi[4]

Abstract

Severe acute respiratory syndrome coronavirus 2 currently represents an ongoing global pandemic. Earlier reports suggested that children were either unaffected by the infection or suffered from a mild course of the disease. However, recently it was established that coronavirus might infect children in severe forms as multi-system inflammatory syndrome, or the so-called Kawasaki-like disease. The true scope of this disease spectrum and the precise consequence of coronavirus infection remains unclear. The current narrative review was planned to analyse studies in which aseptic meningitis was an initial presentation of the multi-system inflammatory syndrome to highlight the importance of coronavirus disease-2019 testing in youngsters presenting with Kawasaki-like symptoms, especially in the presence of a confirmed history of contact with a positive case. Therefore, a high suspicion index is needed to diagnose important presentation of coronavirus disease-2019 in childhood. This current review critically discusses the diversity in clinical presentation, guidelines for the diagnosis, and up-to-date treatment strategies.

Keywords: COVID-19, SARS-CoV-2, Multisystem inflammatory syndrome.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection had spread quickly throughout the globe.[1] Though coronavirus disease 2019 (COVID-19) appears to be milder in children than in adults, severe forms and diverse presentations have lately been documented. Since April 2020, there have been international reports of COVID-19-related severe consequences in formerly healthy children who have been hospitalised with cardiogenic shock or Kawasaki disease-like presentations that were temporarily linked with SARS-CoV-2 infections.[2,3] Different terms have been used to describe this severe presentation. It has been named the Paediatric Multi-system Inflammatory Syndrome temporarily associated with COVID-19 (PIMS-TS) in the United Kingdom, and the Multisystem Inflammatory Syndrome associated with COVID-19 (MIS-C) in the United States.[4] Fever, severe sickness and involvement of two or more body organs, in addition to lab findings of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection characterise the clinical presentation of MIS-C. Some characteristics of MIS-C are similar to those of the Kawasaki disease (KD), toxic shock syndrome and secondary haemophagocytic lymphohistiocytosis/ macrophage activation syndrome.[5] The diagnosis of MIS-C is usually made once the patient fulfils the World Health Organisation (WHO) or the Centres for Disease Control and Prevention (CDC) diagnostic criteria.[6,7] Neurological manifestations are increasingly being described in children with MIS-C, and the cause of the increased frequency remains unknown. The mechanism, however, may differ. Some postulated cerebrovascular thromboembolism was found in adult COVID19 cases.[8] Others proposed that the neurological symptoms were caused by SARS-CoV-2 directly invading the central nervous system (CNS). Laboratory findings demonstrate the angiotensin-converting enzyme 2 (ACE2) expression in both neurons and glial cells in primary host cells, which supports the final theory.[9] The real magnitude of the clinical spectrum of disease and the precise impact of SARS-CoV-2 infection is unknown. It is also unknown whether SARS-CoV-2 can be considered a trigger for KD development or whether KD exhibited unusual and atypical clinical symptoms through the SARS-CoV-2 pandemic.

The current narrative review was planned to summarise the most important clinical, diagnostic and therapeutic approaches for this serious COVID-19-associated illness.

MIS-C definition: Some people may meet all or some of the KD criteria, but they ought to be documented to match the case description for MIS-C. The diagnosis should be considered in any evidence of SARS-CoV-2 infection in a juvenile fatality. The definition of MIS-C is based on three main pillars.

These include any case aged <21 years complaining of fever, laboratory evidence of inflammation, and clinically

[1]Department of Paediatrics, [2]Department of Obstetrics and Gynaecology, Mustansiriyah University, Baghdad, [3]Department of Paediatrics, Central Child Teaching Hospital, Baghdad, [4]Department of Oral maxillofacial Medicine, Karbala University, Karbala, Iraq.

Correspondence: Nabeeha Najatee Akram.
Email: nabiha@uomustansiriyah.edu.iq

severe disease requiring hospital admission with multisystem (>2) comorbidity involving heart, kidney, lungs, blood, gastrointestinal tract, skin or neurology. Besides, there are no other possible diagnoses explaining the clinical picture. Also, there is positivity for new-onset SARS-CoV-2 infection by Reverse transcription polymerase chain reaction (RT-PCR), infection, serology or antigen testing, or established contact with a suspected or positive COVID-19 case within the preceding month.[10]

It should be noted that fever has to be >38°C for ≥24 hours or a report of subjective fever lasting >24 hours. As for the inflammatory laboratory results, they include, but not confined to, erythrocyte sedimentation rate (ESR), increased C-reactive protein (CRP), D-dimer, ferritin, fibrinogen, lactic acid dehydrogenase (LDH), procalcitonin, raised neutrophils, decreased lymphocyte or interleukin 6 (IL-6) and decreased albumin.[10]

Clinical presentation of MIS-C: In addition to the persistent fever, inflammation proved by lab testing, and signs of organ dysfunction or shock, a broad spectrum of presentations has been described. Common symptoms include Kawasaki-like disease: inflamed red eye, hand and feet appearing swollen and red, rash, lips may appear red and fissured, and lymphadenopathy. Also, enlargement and aneurysms of coronary arteries have been reported in some children.[5,11] Some children have gastrointestinal symptoms, such as being nauseous and have abdominal pain, loose stools, while others had inflammation of the colon or the liver. Some presented with acute toxic shock syndrome-like features with signs of impaired cardiac output and over-activation of the inflammatory cascade. Thrombosis or impaired renal function have also been reported. Others complained of breath shortness, implying congestive heart failure or pulmonary embolism. Chest symptoms, like COVID-19 adult infection, are not necessarily present in paediatric cases with MIS-C.[11,12] The neurological presentation was reported in young age group with COVID-19 manifesting as new symptoms of neurological nature involving both the central and peripheral nervous systems (PNS). CNS involvement may be presented as headache, irritability, meningism, confusion ad seizure.[12,13]

Laboratory and imaging testing: Since the majority of the signs and symptoms of MIS-C are not specific, the diagnosis should be based on a strong index of suspicion and prudent clinical judgment, taking into consideration the patient's history, the intensity of organ involvement, the degree of inflammatory markers, and other potential mimickers.[13]

The assessment and management of the presenting symptoms include, but are not limited to, the following:[11]

1. If either a chest scan, or an electrocardiogram (ECG), or a Troponin test show abnormality, a paediatric cardiologist should be consulted, and further diagnostic testing for myocardial damage, comprising echocardiogram and/or cardiac magnetic resonance imaging (MRI) should be undertaken

2. Extensive laboratory testing in patients with neurological symptoms includes pro-B-type natriuretic peptide (pro-BNP), triglyceride (TG) levels, creatine kinase (CK), amylase, urine and blood culture, D-dimer, prothrombin time (PT, partial thromboplastin time (PTT), international normalized ratio (INR), CRP), ferritin, LDH, comprehensive metabolic screen, and fibrinogen brain scans.

3. COVID-19 screening should always be combined with an RT-PCR test and serology. If all serology tests are negative at first, they may need to be redone. Before the delivery of intravenous immunoglobulin (IVIG), serological testing must be performed.

Treatment of MIS-C: The therapeutic aims related to MIS-C are to minimise systemic inflammation, regain organ function, cut mortality, and lower the likelihood of long-term complications, such as the formation of a coronary artery aneurysm or chronic cardiac failure.[5]

There is yet no evidence about the most effective therapy for MIS-C.[14,15] Because of the wide spectrum of clinical presentations, there is no consensus regarding the management strategies of MIS-C. Nevertheless, since the clinical manifestation of MIS-C overlaps to some degree with that of KD, the standard protocols for managing cases with KD is being used for MIS-C cases as well.[16]

Compared to acute COVID-19 infection in children, patient with MIS-C are usually worse off, with over 60% requiring critical care support.[3] Choice of treatments is usually indicated individually, including IVIG, glucocorticoids and biological medications.[16]

In MIS-C, a graded approach to immunomodulatory therapy is strongly suggested. First-line agents include IVIG and glucocorticoids.[17-20] Nevertheless, there is currently inadequate data to assess the effectiveness of IVIG and glucocorticoids in MIS-C or to decide whether these therapies should be administered separately, or in combination.[15] The therapeutic value of plasmapheresis in children with MIS-C is unclear and carries a high risk of complicationss.[12]

Prognosis: A high number of MIS-C or KD is reported in the paediatric age group. Since May 14, 2020, The CDC has announced MIS-C to be a reportable disease and

provided a case definition.[8]

The diversity in MIS-C clinical presentation may lead to a delay in diagnosis or misdiagnosis. Many cases of MIS-C were initially diagnosed as a case of aseptic meningitis based on clinical signs and the result of lumbar puncture. However, when other MIS-C parameters became obvious, like the presence of a positive history of contact with confirmed COVID-19 case(s) and a positive serological test or positive PCR for COVID-19, the diagnosis of MIS-C is usually made.

To date, there is uncertainty about the prognosis of a patient diagnosed with MIS-C. This is because the clinical entity is new, and no sufficient long-term follow-up studies have been done yet.[21] Although survival rates are high, death has been documented.[22] Long-term consequences of MIS-C are unknown.[13] According to studies, the mean paediatric intensive care unit (PICU) stay was six days, and all cases were discharged in excellent health once their clinical symptoms improved. Even though most patients with this condition suffer from cardiac issues and require PICU care, they can recover with adequate therapy.[23-25]

In 2020, a study comprised 46 children hospitalised with MIS-C who were evaluated in a multidisciplinary follow-up clinic following discharge; common clinical sequelae included muscular weakness, reduced exercise capacity, anxiety and emotional difficulties. Laboratory changes at six months in the same study showed normalisation of previously elevated inflammatory and cardiac markers, while 90% of patients remained seropositive for SARS-CoV-2.[26]

Sufficient data is not available regarding medium-term and long-term outcome of MIS-C. However, a study found that in all patients presenting with impaired cardiac function without aneurysm, recovery was achieved by day 74 and all blood tests, including lymphocytes, neutrophils, platelets, creatinine, ferritin, and alanine transaminase (ALT), were normal by day 50 following admission.[26,27]

Conclusion

COVID-19 had a wide range of clinical presentations. New-onset neurological symptoms in previously healthy children could indicate an MIS-C presentation. The review highlights the importance of COVID-19 testing among children with MIS-C, especially in the presence of a positive history of contact with a confirmed case.

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References

1. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422-6. doi: 10.15585/mmwr.mm6914e4.
2. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-8. doi: 10.1016/S0140-6736(20)31094-1.
3. Radia T, Williams N, Agrawal P, Harman K, Weale J, Cook J, et al. Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev 2021;38:51-7. doi: 10.1016/j.prrv.2020.08.001.
4. Nakra NA, Blumberg DA, Herrera-Guerra A, Lakshminrusimha S. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. Children (Basel) 2020;7:69. doi: 10.3390/children7070069.
5. World Health Organization. Multi-system inflammatory syndrome in children and adolescents temporally related to COVID-19. [Online] 2020 [Cited 2021 August 21]. Available from URL: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
6. Centers for Disease Control and Prevention (CDC). Resources for Emergency Health Professionals. [Online] 2020 [Cited 2021 August 21]. Available from URL: https://emergency.cdc.gov/health-professionals.asp
7. Chen TH. Neurological involvement associated with COVID-19 infection in children. J Neurol Sci 2020;418:e117096. doi: 10.1016/j.jns.2020.117096.
8. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. ACS Chem Neurosci 2020;11:995-8. doi: 10.1021/acschemneuro.0c00122.
9. Centers for Disease Control and Prevention (CDC). Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C). [Online] 2021 [Cited 2021 August 21]. Available from URL: https://www.cdc.gov/mis/hcp/index.html
10. American Academy of Pediatrics (AAP). Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance. [Online] 2021 [Cited 2021 August 21]. Available from URL: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/
11. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA Neurol 2020;77:1440-5. doi: 10.1001/jamaneurol.2020.2687.
12. Cattalini M, Taddio A, Bracaglia C, Cimaz R, Paolera SD, Filocamo G, et al. Childhood multisystem inflammatory syndrome associated with COVID-19 (MIS-C): a diagnostic and treatment guidance from the Rheumatology Study Group of the Italian Society of Pediatrics. Ital J Pediatr 2021;47:24. doi: 10.1186/s13052-021-00980-2.
13. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-

19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020;20:e276-88. doi: 10.1016/S1473-3099(20)30651-4.

14. 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 1. Arthritis Rheumatol 2020;72:1791-805. doi: 10.1002/art.41454.
15. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. 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. doi: 10.1161/CIR.0000000000000484.
16. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771-8. doi: 10.1016/S0140-6736(20)31103-X.
17. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094. doi: 10.1136/bmj.m2094.
18. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. JAMA 2020;324:294-6. doi: 10.1001/jama.2020.10374.
19. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series. J Pediatric Infect Dis Soc 2020;9:393-8. doi: 10.1093/jpids/piaa069.
20. Son MBF, Friedman K. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) management and outcome. In: Fulton DR, Kaplan SL, Sundel R, Randolph AG, TePas E, eds. [Online] 2021 [Cited 2021 August 21]. Available from URL: https://www.uptodate.com/contents/covid-19-multisystem-inflammatory-syndrome-in-children-mis-c-management-and-outcome
21. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA 2020;324:259-69. doi: 10.1001/jama.2020.10369.
22. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074-80. doi: 10.15585/mmwr.mm6932e2.
23. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection. Pediatr Infect Dis J 2020;39:e340-6. doi: 10.1097/INF.0000000000002888.
24. Sinaei R, Hosseininasab A, Jafari M, Eslami S, Parvaresh S. The Multisystem Inflammatory Syndrome of Childhood (MIS-C). Indian J Pediatr 2021;88:484. doi: 10.1007/s12098-020-03617-0.
25. 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;5:473-82. doi: 10.1016/S2352-4642(21)00138-3.
26. Nori W, Hameed BH, Thamir AR, Fadhil A. COVID-19 in Pregnancy: Implication on Platelets and Blood Indices. Rev Bras Ginecol Obstet 2021;43:595-9. doi: 10.1055/s-0041-1733912.
27. Davies P, du Pré P, Lillie J, Kanthimathinathan HK. One-Year Outcomes of Critical Care Patients Post-COVID-19 Multisystem Inflammatory Syndrome in Children. JAMA Pediatr 2021;175:1281-3. doi: 10.1001/jamapediatrics.2021.2993.