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CASE REPORT

Multisystem inflammatory syndrome in children (MIS-C) in the paediatric intensive care unit

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Abstract

Currently the world is facing a pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although most children and adolescents are asymptomatic or only have mild symptoms during the acute stage of infection, a severe post-infectious syndrome may occur several weeks after a SARS-CoV-2 infection, known as multisystem inflammatory syndrome in children (MIS-C). The clinical symptoms of MIS-C mimic Kawasaki disease, with fever, a maculopapular rash, conjunctivitis, peripheral oedema and palmar erythema. However, different to Kawasaki disease, many MIS-C patients primarily present with gastrointestinal symptoms or cardiovascular involvement requiring vasopressor or inotropic support.

Introduction

We are currently facing a severe global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In contrast to adults, most children who become infected with this virus are asymptomatic or only have mild symptoms during the acute stage of the infection.[1,2] However, there have been an increasing number of reports describing a severe post-infectious syndrome in children which may occur several weeks after SARS-CoV-2 infection, known as multisystem inflammatory syndrome in children (MIS-C).[3] MIS-C is characterised by clinical characteristics mimicking Kawasaki disease, with fever, a maculopapular rash, conjunctivitis, peripheral oedema and palmar erythema. However, in contrast to Kawasaki disease, patients more often have significant gastrointestinal symptoms and cardiogenic shock. We describe two critically ill patients with MIS-C associated with SARS-CoV-2 infection, admitted to the paediatric intensive care unit (PICU).

Case 1

An 8-year-old, previously healthy boy presented after seven days of vomiting, diarrhoea, abdominal pain and high-grade fever. Eight weeks earlier his mother had been infected with SARS-CoV-2. At initial presentation to a general hospital, his vital signs showed tachypnoea, oxygen saturation of 98% in room air, sinus tachycardia (165 beats/min), blood pressure 109/66 mmHg, prolonged capillary refill time of 3 seconds and a temperature of 39.8°C. The patient appeared ill with tenderness to palpation in the right lower abdominal quadrant. Abdominal MRI showed a thickened appendix wall (8 mm) with some adjacent fluid. Acute appendicitis was suspected and a laparoscopy was performed. However, the appendix appeared only mildly inflamed, insufficiently explaining the clinical presentation. The following day, he developed conjunctivitis, palmar erythema and cracked lips and his condition deteriorated, with tachypnoea, tachycardia and hypotension for which the patient was transferred to the PICU. Laboratory testing showed elevated levels of C-reactive protein (260 mg/l), leukocyte count (19.3 x 10^9/l), D-dimer (4.06 mg/l) and ferritin (1128 µg/l). The echocardiogram showed borderline low left ventricular function with a shortening fraction of 24-28% and biplane left ventricular ejection fraction of 32%. Troponin (46 ng/l) and NT-proBNP (19,795 ng/l) were elevated, compatible with heart failure. Inotropic support with milrinone and noradrenalin was initiated. Because of oedema and increasing oxygen demand, diuretics were given. Due to mucocutaneous, gastrointestinal and cardiac system involvement, MIS-C was suspected and methylprednisolone pulse therapy, intravenous immunoglobulins (IVIG) and carbasalate calcium were started. Antibody testing for SARS-CoV-2 (SARS-CoV-2 IgG) was positive, confirming the diagnosis of MIS-C. The patient's clinical condition improved one day after starting IVIG and methylprednisolone pulse therapy. After seven days he was discharged home in a good condition on prednisolone

(tapering schedule) and carbasalate calcium maintenance therapy. At outpatient follow-up eight weeks after discharge, the echocardiogram showed good ventricular function and normal diameters of de coronary arteries. Carbasalate calcium was stopped. A cardiac MRI is scheduled to be performed six months after discharge.

Case 2

A 16-year-old girl without significant medical history was admitted to hospital after she had collapsed at home. Three weeks prior to admission she had tested positive for SARS-CoV-2 after she had presented with fatigue and mild respiratory symptoms which had resolved spontaneously. In the week prior to admission, she had suffered from a fever, sore throat, headaches, vomiting and diarrhoea for which the general physician prescribed antibiotics and antiemetics under the suspicion of a pharyngitis. On presentation she showed signs of circulatory failure with a tachycardia (159 beats/min), hypotension (80/60 mmHg), prolonged capillary refill time (4 seconds) and cold extremities. She showed no response to repeated fluid challenges and was transferred to the PICU for inotropic treatment. Ceftriaxone and clindamycin were initiated to cover sepsis of unknown origin and toxic shock syndrome. Lab testing showed elevated inflammatory markers (CRP 195 mg/l, ferritin 2834 µg/l), cardiac enzymes (troponin 76 ng/l, NT-proBNP 24603 ng/l) and transaminases (ASAT 136 U/l, ALAT 80 U/l). Echocardiography showed poor left ventricular function with a shortening fraction of 16%, which deteriorated to 10% the next day, and biplane left ventricular ejection fraction of 23%, but no dilation of the coronary arteries. She was treated with milrinone and noradrenaline. Methylprednisolone pulse therapy, immunoglobulins and carbasalate calcium were started under the diagnosis of MIS-C. SARS-CoV-2 IgG also turned out positive at admission. Her condition improved and after five days she was transferred to the general ward. At day six her cardiac function was normal with a shortening fraction of 31%. After discharge, symptoms of palpitations and chest pain occurred, for which a Holter registration was performed. This showed premature ventricular contractions (5.3% of total beats), which were monomorphic and occurred solitarily. Cardiac exercise stress testing revealed premature ventricular contractions both during exercise and during the resting phase. A cardiac MRI is scheduled to be performed six months after discharge.

Discussion

During the first COVID-19 wave, several papers appeared reporting a severe inflammatory syndrome with Kawasaki disease-like features occurring in previously healthy children who had evidence of recent infection with SARS-CoV-2.[4,5] Since the first reports, an increasing number of children and adolescents have been reported with similar manifestations.[3] The World Health Organisation (WHO) and US Centers for Disease Prevention and Control (CDC) defined this hyperinflammatory syndrome and termed it MIS-C (*table 1*).[6,7] Since then, in the Netherlands, numerous children have been reported with clinical features matching MIS-C, some requiring intensive medical care due to circulatory insufficiency.[8]

MIS-C is most likely not mediated by direct viral invasion, but coincides with the development of an acquired immune response to SARS-CoV-2 since the interval from SARS-CoV-2 exposure to onset MIS-C symptoms is on average 4-6 weeks.[3,9] In addition, only one third of the reported MIS-C cases tested positive for SARS-CoV-2 by RT-PCR, whereas most cases had positive serology for SARS-CoV-2, suggesting MIS-C is related to a post-viral immune-mediated inflammatory process.[3]

Although many MIS-C patients meet all or almost all the criteria for Kawasaki disease, there are several clinical features that distinguish MIS-C from Kawasaki disease. Many patients with MIS-C primarily present with gastrointestinal symptoms (severe abdominal pain, vomiting and diarrhoea, in some patients mimicking appendicitis) and neurological manifestations (headache, lethargy).[9] Cardiovascular involvement is seen in both Kawasaki disease and MIS-C. More than 80% of MIS-C patients present with highly elevated levels of NT-proBNP and troponin, which indicates myocardial injury.[3,9,10,11] On echocardiogram, left ventricular dysfunction is observed in 30-100% of the patients seen by a paediatric cardiologist, depending on the definition and inclusion criteria.[3,10,11] Shock is frequently observed in children with MIS-C and can be either vasoplegic refractory to volume resuscitation, cardiogenic shock or a combination of both, leading to high amounts of vasopressor or inotropic support.[12] More than 50% of the children with MIS-C present with cardiogenic shock, whereas only 5% of the children with Kawasaki disease present with a more severe clinical phenotype called Kawasaki Disease Shock Syndrome (KDSS).[3,9,13] KDSS has a remarkable overlap with the features of MIS-C, including older age at presentation, atypical presentation with multiple organ involvement and ventricular dysfunction.[14] In addition, coronary artery aneurysms, a common feature of Kawasaki disease, are less frequently described in MIS-C patients. In 6-24% of MIS-C patients coronary dilatation or aneurysms have been described, in most of whom only mild coronary artery dilatation was seen.[10,11]

In addition to a wider clinical spectrum, the epidemiology of MIS-C differs from that of Kawasaki disease. The majority of MIS-C patients are of Hispanic/Latino and non-Hispanic Black origin, whereas children of Asian ancestry have the highest incidence of Kawasaki disease.[3,7,9,15,16] Moreover, MIS-C generally occurs in older children and adolescents with an average age of eight years, in contrast to Kawasaki disease commonly occurring in children under five years of age, with a peak incidence at 10 months of age.[3,7,9,15,16]

Table 1. Definition of multisystem inflammatory syndrome in children (MIS-C)

Criteria WHO [6]	Criteria CDC [7]
Children and adolescents 0–19 years of age with fever >3 days AND **two** of the following: • Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); • Hypotension or shock; • Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP); • Evidence of coagulopathy (by PT, PTT, elevated d-dimers); • Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19	An individual aged <21 years presenting with fever*, laboratory evidence of inflammation**, and evidence of clinically severe illness requiring hospitalisation, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, haematological, gastrointestinal, dermatological or neurological) AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms * *Fever ≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours* ** *Including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin*

The overlapping clinical features between Kawasaki disease, KDSS and MIS-C suggest that they may share similar pathophysiological pathways and this might explain why these patients respond similarly to the same therapies. Most MIS-C cases are treated with intravenous immunoglobulin with or without aspirin, similar to the standard protocol for Kawasaki disease.[3] The addition of glucocorticoids to the treatment is recommended, especially in more severe cases.[17] The American College of Rheumatology made an overview to provide guidance on the management of MIS-C, based on currently available evidence coupled with expert opinion, which will be revised as further evidence becomes available.[18] Also, treatment recommendations by the Dutch Paediatric Society have been formulated.[19]

Conclusion

MIS-C is a life-threatening complication of a SARS-CoV-2 infection that affects multiple organ systems in predominantly previously healthy children and adolescents. This syndrome has many similarities with the well-known Kawasaki disease. Remarkable differences are the high percentage of children with shock due to cardiac failure, older age of presentation and in most cases multi-organ involvement including gastrointestinal symptoms. The precise pathogenesis of MIS-C is largely unclear and further studies and follow-up of MIS-C patients are needed to provide insight into the pathophysiology, clinical outcomes and prognosis, and to define an evidence-based management of this novel disease.

Disclosures

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Informed consent was obtained from the patients family for the publication of this case report.

References

1. X. Lu, L. Zhang, Chinese Pediatric Novel Coronavirus Study Team et al. SARS-CoV-2 infection in children. New Engl J Med. 2020;382:1663-5.
2. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. JAMA Pediatr. 2020;174:882-9.
3. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20:e276-e288.
4. PICS Statement: increased number of reported cases of novel presentation of multisystem inflammatory disease. Paediatric Intensive Care Society, April 2020. (accessed December 29, 2020, at https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf)
5. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Royal College of Paediatrics and Child Health, May 2020. (accessed December 29, 2020, at https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf)
6. Multisystem inflammatory syndrome in children and adolescents with COVID-19. World Health Organization, May 2020. (accessed December 29, 2020, at www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19)
7. Multisystem inflammatory syndrome. Centers for Disease Control and Prevention, 2020. (accessed December 29, 2020, at https://www.cdc.gov/mis-c/hcp/)
8. Blink M, Buddingh EP, Filippini LHPM, Brinkman DMC, Joosten SA, Klein RH. Covid-19-geassocieerde hyperinflammatie. Ned Tijdschr Geneeskd. 2020;164:D5348
9. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020;383:334-46.
10. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180:307-22.

11. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe. Circulation. 2021;143:21-32.
12. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020,395:1607-8.
13. Matsubara D, Kauffman HL, Wang Y et al. Echocardiographic Findings in Pediatric Multisystem Inflammatory Syndrome Associated With COVID-19 in the United States. J Am Coll Cardiol. 2020;76:1947-61.
14. Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123:e783-9.
15. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics. 2003;112(3 Pt 1): 495-501.
16. McCrindle BW, Rowley AH, Newburger JW, 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-e999.
17. Ouldali N, Toubiana J, Antona D, et al. Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children. JAMA. 2021;325:855-64.
18. Henderson LA, Canna SW, Friedman K et al. American College of Rheumatology. Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2 and Hyperinflammation in COVID-19. Version 1. Arthritis Rheumatol. 2020;72:1791-805.
19. Buddingh E, Witteveen T. Overzicht ten aanzien van diagnostiek, behandeling en follow-up bij COVID-19 geassocieerd Multisysteem Inflammatoir Syndroom (MIS-C). NVK. 2021 juni.