Case Report

Case series of Multisystem Inflammatory Syndrome in Children (MIS-C) after a SARS-CoV-2 infection

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Keywords

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Abstract

Background

Multisystem inflammatory syndrome in children (MIS-C) is an entity in which children develop fever, raised inflammatory parameters, abdominal complaints and/or Kawasaki-like symptoms with signs of decreased cardiac function, weeks after a primary infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Complications include shock and coronary artery aneurysms. Off-label use of intravenous immunoglobulins and corticosteroids have shown good results in previous reports.

Case series

We present our experience of five patients who met criteria for MIS-C. Their presentation varied widely; three patients had abdominal complaints with a non-specific presentation and the others had Kawasaki-like symptoms. All had highly elevated inflammatory parameters and cardiac enzyme levels. Three showed intra-abdominal signs of inflammation. Two patients needed transfer to an intensive care unit. They were all treated with intravenous immunoglobulins after which all patients recovered quickly with no residual problems to date.

Conclusions

Our cases are in line with current evidence that clinical presentation of MIS-C is extremely variable, and evolution is favourable after treatment with intravenous immunoglobulins. Further research is necessary to substantiate current guidelines and to analyse possible links we have encountered between developing MIS-C and ethnic background, environment, and specific SARS-CoV-2 strains.

Introduction

Reports from the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic suggested children to be less frequently and less severely affected by this viral infection in comparison to adults. They also stated that children were rarely in need of intensive care treatment. However, from April 2020 onwards, reports emerged of children seriously affected by hyperinflammatory shock with multi-organ involvement seemingly associated with an infection by the novel virus. Patients typically presented four to eight weeks after a presumed primary SARS-CoV-2 infection with acute symptoms of fever, abdominal complaints (pain, vomiting and diarrhoea), signs of shock, rash, conjunctival injection, neurologic symptoms and sometimes respiratory symptoms (1,2). Laboratory investigations revealed raised inflammatory parameters. The new entity showed features partially similar to those of Kawasaki disease (KD), toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome (3). Based on these reports, a preliminary definition was created by the World Health Organisation (WHO) in May 2020, labelling the condition as "Multisystem Inflammatory Syndrome in Children and adolescents" (MIS-C) (4). According to the WHO definition, cases of children and adolescents between 0 and 19 years of age with fever for a period of at least three days, in combination with specifically described clinical features and raised inflammatory parameters, and evidence of a (past) SARS-CoV-2 infection or likely contact with patients with such an infection, meet the criteria for MIS-C.

In analogy to KD, patients are favourably treated with intravenous immunoglobulins (IVIG) and corticosteroids as shown by some studies (5,6). Treatment nearly always provided a positive outcome, but patients could die in extremely severe cases (<1%). A frequently seen complication was the development of coronary artery aneurysms and ventricle dysfunction, though resolution of these cardiac abnormalities was seen in most patients within months (7–11). In this article we presented our experience with MIS-C in a case series of five children over the course of two months and reviewed the literature on some topics of interest.

Case Series

Over the course of 2 months, we saw a total of five cases of MIS-C in the paediatric department of our general hospital in the suburbs of Antwerp. In the subsequent paragraphs, we discussed them one-by-one and an overview of the cases can be found in Table 1. Diagnosis and treatment plan were made based on the guidelines created by the Belgian Institute of Health (Sciensano), by the PIMS-TS National Consensus Management Study Group in the United Kingdom and by specialists of New York-Presbyterian Morgan Stanley Children's Hospital of New York City in the United States (12).

The first patient was a 15-year-old girl who presented to the emergency department because of abdominal pain for a period of five days, vomiting and fever. Based on a thorough first assessment, the preferred initial diagnosis was sigmoiditis for which she was admitted and treated with intravenous antibiotics (amoxicillin-clavulanic acid). Due to aggravation of pain the following day, an explorative laparoscopy was performed the same day, which showed intraperitoneal free fluid and an oedematous terminal ileum. It was decided not to adjust the initial therapy. Two days later her clinical state worsened dramatically, with a drop in blood pressure (100/60 mmHg), signs of poor circulation and respiratory distress. Crepitations were heard on auscultation and a computed tomography scan revealed a bilateral pneumonia. The antibiotic therapy was switched to piperacillin/tazobactam (4 grams four times a day). By giving a fluid bolus and supplemental oxygen, it was tried to stabilise her clinical condition, but her situation remained precarious.

She was transferred to the paediatric intensive care unit (PICU Paola Children Hospital, Antwerp, Belgium and subsequently PICU UZ Ghent, Ghent, Belgium). An echocardiography showed a decreased left ventricle function (fractional shortening 15-17%, ejection fraction 30-50%) and a dilated left coronary artery (LCA 3.3 mm). Cardiac enzymes were elevated as well, with a high-sensitivity troponin T (HsTropT) level of 47.2 ng/L (normal value <12 ng/L) and a N-terminal pro-brain-type natriuretic peptide (NT-pro-BNP) level of 24518 pg/mL (normal value <217 pg/mL), supporting a diagnosis of myocarditis. She was tested positive for SARS-CoV-2 by PCR a few days before admission and antibodies were tested positive during admission. The patient was given a single dose of IVIG (2 g/kg) and a high dose of methylprednisolone (20 mg/kg) and was started on intravenous acetylsalicylic acid (250 mg once daily). To maintain an acceptable blood pressure, she briefly received inotropic/vasodilating treatment. With this treatment plan, her clinical state gradually improved over the following days, with full recovery of the cardiac function and relief of the respiratory distress. At follow-up three weeks after discharge she was generally well, except for mild persisting anaemia (haemoglobin 10.0 g/dL) and some fatigue. Cardiac follow-up one month after discharge showed normalisation of the left ventricle function and coronary arteries.

The second case was a teenage boy who's presenting symptoms were abdominal pain and diarrhoea for three days, fever, anorexia, headache and fatigue. He had a non-toxic appearance, dull heart sounds and a painful examination of the right fossa with some muscle defence. An abdominal ultrasound was suggestive for acute appendicitis. The initial laboratory results showed minimally elevated leukocytes (10.8 × 10^9/L, reference 4.4-10.6 × 10^9/L), C-reactive protein (CRP) of 114.5 mg/L (normal value <5 mg/L) and normal renal and liver function values. Awaiting the SARS-COV-2 antibody and PCR test results it was decided to maintain expectant management and the boy was kept under observation. Over the following two days he remained febrile, his abdominal pain worsened and he vomited several times. The patient developed tachycardia but his blood pressure remained stable. Laboratory testing confirmed a further elevation of inflammatory parameters (leukocytes 11.3 × 10^9/L, CRP 207 mg/L, erythrocyte sedimentation rate 104 mm/h (normal <15), ferritin 598 µg/L (normal value 30-400 µg/L)), mildly prolonged coagulation time (international normalised ratio 1.32, reference 0.87-1.20), positive SARS-CoV-2 antibodies and mildly elevated cardiac enzymes (HsTropT 19.6 ng/L, NT-pro-BNP 2196 pg/mL). Since the patient met the criteria for MIS-C, treatment with IVIG (2 g/kg), IV cefotaxime (100 mg/kg/day) and subcutaneous heparin (2000 IU twice daily) was started. The next day his abdominal complaints improved significantly. The boy was discharged following full recovery after eleven days. At follow-up one week later, he did not have any complaints and showed normalised inflammatory parameters.

Case number three was a 10-year-old girl who presented at the outpatient clinic, after having been treated for the last five days with amoxicillin orally (500 mg three times daily) for a persisting swelling in the neck, together with stomach ache, vomiting and anorexia. On physical examination she appeared well but had a pharyngitis and several enlarged and tender cervical lymph nodes. Her laboratory results showed signs of severe inflammation (leukocytes 16.5 × 10^9/L, CRP 195 mg/L, ferritin 659 µg/L) and elevated cardiac enzymes (HsTropT 152 ng/L, NT-pro-BNP not performed). The girl was admitted to the hospital and her antibiotic regimen was switched to amoxicillin-clavulanic acid IV (100 mg/kg/day). She was tested positive for SARS-CoV-2 on PCR on admission and antibodies came back positive the next day.

During observation the abdominal complaints worsened and vomiting persisted. Her abdomen was tender. An abdominal ultrasound showed signs of cholecystitis as well as enteritis and free intraperitoneal fluid. An echocardiography showed signs of a mild myopericarditis without coronary involvement. The girl received a one-time dose of IVIG (2 g/kg). Additionally, she was started on acetylsalicylic acid (4 mg/kg/day) as preventive antithrombotic therapy, and lisinopril (2.5 mg/day) was started to reduce cardiac afterload. For the abdominal symptoms she was started on pantoprazole IV (40 mg once daily) and ondansetron IV when necessary (0.1 mg/kg/dose). Over the next few days, the clinical situation stabilised, oral intake resumed and symptoms improved gradually. She was discharged after eleven days. She remained complaint-free at follow-up up to a month after discharge; the echocardiographic findings were normalised seven days after discharge.

The fourth case concerned a boy, seven years of age, who presented to the emergency department with fever for the last five days, abdominal pain, vomiting and diarrhoea. On examination he seemed uncomfortable due to pain, had a generally tender abdomen, bilateral non-purulent conjunctivitis and enlarged tonsils with white exudate. He had elevated inflammatory laboratory parameters (leukocytes 11.1 × 10^9/L, CRP 191.8 mg/L), acute kidney injury presumably secondary to hypoperfusion (creatinine 2.26 mg/dL (reference 0.29-0.47), urea 105.4 mg/dL (reference 15-36 mg/dL)), showed a mildly elevated HsTropT level of 36 ng/L and had positive SARS-COV-2 antibodies. The patient was treated with IVIG (2 g/kg), acetylsalicylic acid (24 mg/kg/day) and IV cefotaxime (100 mg/kg/day). The acute kidney injury resolved quickly after fluid substitution.

A throat swab tested positive for *Streptococcus pyogenes*, sensitive to penicillin. Haemocultures remained negative. Antibiotics were switched to oral amoxicillin-clavulanic acid (50 mg/kg/day) to treat this infection and cover possible other microbiological pathogens. After the initiation of treatment for MIS-C the clinical picture improved rapidly. He was discharged after six days of admission, fully recovered from his physical complaints. He was still complaint-free at follow-up at ten days and one month after discharge.

The last patient was a 6-year-old boy, who presented to the emergency room because of malaise, fever, throat pain, vomiting, diarrhoea, anorexia, myalgia, headache and itching of the feet for the last five days. He was alert, but groaned and shivered, and looked pale. His lips were crackled, he had a raspberry tongue and a red throat with enlarged tonsils. A warm, erythematous rash was apparent, predominantly on his neck, palms and soles. Laboratory testing showed elevated inflammatory markers (CRP 177.3 mg/L, ferritin 975 µg/L, no leucocytosis), acute kidney injury (creatinine 2.26 mg/dL, urea 105.4 mg/dl), thrombocytopenia (36 × 10^9/L), and an elevated HsTropT level of 59.6 ng/L. Initially he was given an intravenous fluid bolus NaCl 0.9% (10 mg/kg) and IV cefotaxime (100 mg/kg/day) was administered. After a positive result for SARS-CoV-2 antibodies, treatment for MIS-C was started with IVIG (2 g/kg), during which the rash expanded and an additional swelling of the right side of the face appeared.

Despite the IVIG administration the clinical situation worsened, with development of tachycardia (130 beats/min), hypotension (79/39 mmHg) and poor peripheral circulation. Therefore, it was decided to transfer him to the PICU (Paola Children's Hospital Antwerp, Belgium). A cardiac ultrasound was performed and showed minimal mitral valve insufficiency, without further signs of myocarditis or the presence of coronary aneurysms. The patient was given an IV fluid bolus NaCl 0,9% (10 mL/kg) and he was started on IV dobutamine (5 µg/kg/min) to support the cardiac function. Additional treatment for MIS-C was initiated with IV methylprednisolone (2 mg/kg/day) and acetylsalicylic acid (2 mg/day). With this treatment there was a positive evolution of the clinical condition. Dopamine infusion could be stopped after three days, and the patient was transferred back to the paediatric ward after five days. Three days later he was discharged from the hospital. Unfortunately, he was subsequently lost to follow-up, but informal (phone) follow up revealed no further complaints.

Discussion

Our case series described five cases of MIS-C patients with various presentations. Diagnosis was based on the definition set by the WHO with the presence of fever, multisystem organ involvement, positive SARS-CoV-2 PCR-test, antigen test or antibodies and laboratory evidence of inflammation. All our patients had a favourable evolution and outcome after treatment with IVIG, with or without the addition of corticosteroids. Only two of our patients showed signs of shock and required intensive care treatment.

Three patients showed cardiac complications on echocardiography, of which one had coronaritis, one myopericarditis and another one mitral valve insufficiency (Table 1). At follow-up all our patients reported full recovery, no recurrence of complaints or new complications.

The initial presentation and working diagnosis of our patients varied widely: sigmoiditis (case 1), appendicitis (case 2), cholecystitis with lymphadenitis colli (case 3), abdominal complaints and conjunctivitis (case 4) and strawberry tongue and rash (case 5). This varied presentation matched the numerous ways of presentation reported in other case reports and articles (1,8,9,13-17). The WHO and Belgian Institute of Health each drew up a classification system for presentation of MIS-C as guidance grouping them in presentation as a Kawasaki-like syndrome, as a non-specific presentation mostly including abdominal symptoms or as signs of cardiac dysfunction with or without shock (4,13,15,18). All the same, diagnosing MIS-C remains challenging, because of this high variety and severity of possible symptoms at presentation (13,15).

Our three patients presenting with predominantly abdominal complaints all showed signs of inflammation on ultrasound like intestinal wall thickening, reactive lymph nodes and free fluid. Many other reported MIS-C patients had signs of intra-abdominal inflammation on different types of imaging as well. Reports by Hameed *et al*. and Morparia *et al*. showed that almost all patients with abdominal complaints who underwent abdominal imaging had abnormalities (19,20). On ultrasound this included predominantly anechoic free fluid, localised inflammatory changes and wall thickening of the bowel (including the right fossa) or gallbladder and mildly enlarged lymph nodes, which was also the case in our cases 1-3. In most of the cases the appendix itself appeared normal. All seven patients described by Morparia *et al.* had hepatomegaly while this was not present in any of our patients and was only sporadically seen by Hameed *et al.*. The combination of the abdominal symptoms and abnormal radiological findings resemble surgical emergencies and thus poses a therapeutic dilemma (21,22). A SARS-CoV-2 antibody and/or PCR test screening for (recent) contact with the virus could help differentiate and prevent unnecessary surgical interventions. Alternatively, a diagnosis of MIS-C should not exclude the presence of other causes of abdominal pain. Lishman *et al*. described three patients with MIS-C who also had a surgically confirmed diagnosis of appendicitis. They suggested that a SARS-CoV-2 infection could facilitate the onset of an appendicitis (23).

Patients 4 and 5 of this series showed signs of KD with conjunctivitis, lymphadenopathy, crackled lips, pharyngitis and a macular rash on neck, hands and feet. Since these patients did not present four out of the five criteria they should be defined as incomplete KD rather than complete KD. MIS-C was first described as a Kawasaki-like disease linked to SARS-CoV-2 (16,24). Since then, many other cases of MIS-C patients with Kawasaki-like symptoms have been described (8,9,17,25,26). However, there are some differences between MIS-C and KD. Compared to complete Kawasaki disease patients affected by MIS-C were generally older and were rather of Black or Hispanic origin instead of Asian origin (8,9). Presentation more often involved abdominal complaints and patients more frequently developed myocardial dysfunction and shock (9). They had different laboratory findings, like a higher white blood cell and neutrophil count, higher levels of inflammatory parameters, more profound anaemia and thrombocytopenia, and a higher elevation of cardiac enzyme levels (8).

The fact that the throat swab from our fourth patient was found positive for Streptococcus pyogenes might lead to the assumption that this was no case of MIS-C. The definition set by the WHO clearly states that no other explanation for the symptoms of a patient should be found. However, the proven bacterial infection in his throat was not sufficient evidence for the symptoms this boy presented with. Streptococcus pyogenes is thought to sporadically cause an incomplete form of KD, but only in cases of severe invasive bacterial illness. The fact that our patient did not show such illness, that he was found to be positive for SARS-CoV-2, and that he reacted to treatment with IVIG, led to the assumption that he suffered indeed from MIS-C.

Since the symptoms and imaging results seemed nonspecific, distinguishing laboratory parameters would be useful. In general, CRP, procalcitonin, ferritin, LDH and D-dimer levels were higher in MIS-C patients compared to non-MISC patients (1,15). Additionally, alanine aminotransferase (ALT) elevations and raised HsTropT and NT-proBNP levels, suggesting cardiac involvement, were more frequently seen and were generally higher in MIS-C than in a non-MISC population with similar presenting symptoms (1,15). In practice however, there is still no cut-off of one parameter that can result in a diagnosis and combination of these parameters remains necessary. Kelly et al. proposed the following as the best cut-off values: CRP 119.6 mg/L, procalcitonin 0.215 ng/mL, ferritin 122 ng/L, D-dimer 924 ng/mL, ALT 25 IU/L, HsTropT 16 ng/L, NT-proBNP 212 pg/mL (15). In our patient population, the blood levels of CRP, ferritin D-dimers and HsTropT met these criteria. ALT elevation above 25 IU/L was only present in two of our patients. Procalcitonin was not determined in our cases. No significant differences in laboratory results between patients with a Kawasaki-like presentation versus those with an non-specific presentation were found, but patients presenting with shock did have significantly higher neutrophil counts and levels of CRP, ferritin, D-dimer, HsTropT and NT-proBNP and lower platelet and albumin levels (8, 27).

We noted that only one of our patients was of European descent. The parents of our cases were born in respectively West Africa (2), Morocco, Suriname and Poland. Multiple retrospective studies have shown patients of African or Hispanic ethnicity to be overrepresented in the MIS-C population compared to what would be expected from population statistics (8, 26–29). The exact aetiology remains elusive, but several reasons have been proposed. There could be a genetic predisposition linked to the ApoE4 genotype as suggested by Goldstein et al. (30). Different social determinants including housing and economic instability in patients from foreign origin might also explain this difference. This was stated as a probable cause in adults, since these populations are also overrepresented in the incidence of severe SARS-CoV-2 infections and hospitalisations (28). However, this speculation is solely based on European, Asian and American studies, as incidence data from either African or South American studies on MIS-C are scarce. If origin would play a role in the chance to develop MIS-C, it would explain our high number of patients from foreign background.

To date we only saw a series of cases in our hospital presenting over a period of two months' time, weeks after the second wave of SARS-CoV-2 infections in Belgium. We wonder why we did not see patients after the peak of the first and the third waves, which have passed for months now. Enquire with colleagues from other hospitals in the area learned that they also found the same peak in incidence, although no truly reliable data have been produced up till now. The possibility of MIS-C cases being missed during the first and third wave seems not plausible given the severity of the disease. We wondered whether lockdown measures leading to prohibition to go to school and thus having a lower chance to get infected with the virus and developing MIS-C might pose an explanation. However, most patients were being infected with SARS-CoV-2 within their own household, which would contradict this. Maybe the seasonal variation in virulence of SARS-CoV-2 could help explain the difference. Specific SARS-CoV-2 strains might increase the risk of developing MIS-C compared to other strains. But up till now, no data about this topic are provided by literature. Hypothetically, because of the similarity with Kawasaki disease which presence and incidence has been associated with tropospheric wind patterns, we also wondered whether an analogous system or other environmental factors could explain our burst of patients (31). Unfortunately, no studies of this type have been performed. We could not find any explanation concerning the link between MIS-C and environmental factors.

Conclusions

By presenting these cases, we aimed to highlight that MIS-C can present through a variety of symptoms that can generally be divided into three groups that have been stated in recent literature: Kawasaki-like; with non-specific (mostly abdominal) symptoms; and with shock and cardiac dysfunction. Because of this variety in symptomatology, it is paramount to search for clues of MIS-C through diagnostic tests, even in patients with less specific complaints. Research is needed to substantiate current guidelines.

The majority of our patients was of non-European descent, as seen in many other reports. Reasons for this are not yet known and should be sought for in future research. It remains remarkable that a peak in incidence in our hospital was only seen after the second wave of SARS-CoV-2 infections in Belgium. A conclusive explanation for this fact cannot be given with present knowledge and should be investigated in the future. Possible links between developing MIS-C and the variability in virulence caused by season or different SARS-CoV-2 strains might be interesting to analyse.

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Competing interests

The authors declare that they have no competing interests.

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Table 1 : *Modified Sarnat scoring system. Predominant clinical features in stage 2 and/or stage 3 are an indication to start with therapeutic hypothermia. From Sarnat et al. Sarnat grading scale for neonatal encephalopathy after 45 years: an update proposal (8). With permission from Elsevier.*

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Female	Male	Female	Male	Male
Age (years)	15	10	10	7	6
Fever > 3 days	2 days monitored, report of 3	yes	2 days monitored, report of 5	yes	Yes
Symptoms according to WHO	muco-cutaneous inflammation; hypotension; coronaritis; elevated HsTropT and NT-proBNP; coagulopathy; abdominal pain	elevated HsTropT and NT-proBNP; coagulopathy; abdominal pain; diarrhoea	myo-pericarditis; elevated HsTropT; coagulopathy; abdominal pain; vomiting	bilateral conjunctivitis; elevated HsTropT; coagulopathy; abdominal pain; vomiting	rash; mucocutaneous inflammation hypotension (shock); mitral valve insufficiency; elevated NT-proBNP; coagulopathy; vomiting and diarrhoea
Elevated inflammatory markers	yes	yes	yes	yes	yes
Other cause of inflammation	no	no	no	*S. pyogenes* tonsillitis	no
Evidence of SARS-COV-2 infection	Ab positive, PCR positive	Ab positive, PCR positive	Ab positive, PCR positive	Ab positive, PCR negative	Ab positive, PCR negative
Therapy*	Amoxicillin-clavulanic acid; piperacilline-tazobactam; IVIG; acetylsalicylic acid; methyl-prednisolone; inotropics	Cefotaxime IV; IVIG; enoxaparine SC; furosemide IV; tube feeding	Amoxicillin-clavulanic acid; IVIG; pantoprazole; ondansetron; acetylsalicylic acid; lisinopril	Cefotaxime IV; IVIG; acetylsalicylic acid; pantoprazole; Vitamin D	Cefotaxime IV; IVIG; dobutamine; acetylsalicylic acid; methyl-prednisolone; esomeprazole;
PICU admission	yes	no	no	no	yes

** Every patient received pain relief and antipyretics on demand and IV fluids depending on oral fluid intake*

HsTropT: *high-sensitivity troponin T;* ***IV:*** *intravenous;* ***IVIG:*** *intravenous immunoglobulins;* ***MIS-C:*** *Multisystem Inflammatory Syndrome in Children and adolescents;* ***NT-proBNP:*** *N-terminal pro-brain-type natriuretic peptide;* ***PICU:*** *paediatric intensive care unit;* ***SARS-CoV-2:*** *severe acute respiratory syndrome coronavirus 2;* ***SC:*** *subcutaneous;* ***WHO:*** *World Health Organisation*