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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN: A NOVEL PRESENTATION OF COVID-19 IN PEDIATRICS

Mariame Lakhrissi[1]*, Soumia Benchekroun[1], Imane Jroundi[2], Naima El Hafidi[1] and Chafiq Mahraoui[1]

[1]Pneumo-Allergology and Infectiology Department (P1), Ibn Sina Children's University Hospital, Rabat, Morocco.
[2]Unit of Research and Training of Public Health, School of Medicine and Pharmacy University Mohammed V, Rabat, Morocco.

***Corresponding Author: Mariame Lakhrissi**
Pneumo-Allergology and Infectiology Department (P1), Ibn Sina Children's University Hospital, Rabat, Morocco.
Email ID:

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ABSTRACT

The pediatric multisystem inflammatory syndrome has been described as a new manifestation of SARS-CoV-2 infection in children and adolescents. We aim through this retrospective study to describe the epidemiological, clinical, biological, therapeutic and evolutionary characteristics of our patients. 16 cases were identified in the pneumo-allergology and infectious diseases department at the children's hospital in Rabat from November 26th, 2020 to February 24th, 2021.The median age was 6.5 years, with a sex ratio = 1.6. Mucocutaneous manifestations were present in all cases. Gastrointestinal symptoms were present in 69% of cases (11 patients), while respiratory symptoms were present in 4 patients (25%). Biologically, inflammatory markers were elevated in all patients. SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) results were negative in all patients, while SARS-CoV-2 serology was positive in 15/16 patient (94%). Cardiac involvement was present in 37% of cases (6 patients) including myocarditis in 19% of cases (3 patients) and coronary involvement in 31% of cases (5 patients). Most of the characteristics of our MIS-C patients were similar to those in the literature, but more studies are needed to confirm these results and better understand this new entity.

KEYWORDS: SARS-CoV-2; Multisystem inflammatory syndrome in children; MIS-C; COVID-19; Children, Kawasaki disease.

INTRODUCTION

Kawasaki disease (KD) is a vasculitis that mainly affects small and medium caliber vessels, with a tropism for coronary arteries. The majority of affected patients are younger than 5 years of age and the incidence varies between countries and the time of year.[1,2] Its etiology remains, to this day, poorly identified; However, there seems to be an immunological theory involving an infectious agent, especially viral, in people who are genetically predisposed.[3-5] These viruses include mainly rhinoviruses and enteroviruses, as well as other viral agents, including coronaviruses.[3,4,6] The later virus or as it' s known as the COVID-19 infection, is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first identified in 2019 in Wuhan, China and quickly spread to become a global pandemic. Evidence suggests that children and adolescents most often develop mild respiratory symptoms, unlike severe forms of symptoms reported in adults.[7-9]; in contrast, severe manifestations associated with multisystem inflammatory syndrome have been recently reported in children and adolescents during this pandemic, some of which are reminiscent of Kawasaki disease, toxic shock syndrome or macrophagic activation syndrome.[10-12] Numerous case definitions for this emerging disease called MIS-C (Multisystem Inflammatory Syndrome in Children) or PIMS (Pediatric Inflammatory Multisystem Syndrome), have been provided[13-15] (Annex 1).

The main objective of this study is to analyze the epidemiological, clinical, biological, therapeutic and evolutionary profile of our patients by comparing it with literature data.

MATERIALS AND METHODS

We have included all children and adolescents (aged ≤ 18 years) who were admitted to the pneumo-allergology and infectious diseases department at the children's hospital in Rabat and met the criteria Kawasaki disease during the covid-19 pandemic period, between November 26th, 2020 and February 24th, 2021.Our hospital is the referral public university hospital center for the Rabat-Salé-Kenitra region.

These patients were admitted as suspects of COVID-19 and whose management was carried out in accordance

with the recommendations of the country's health ministry regarding this condition.

The collection of clinical, para-clinical, therapeutic and evolutionary elements was made by analyzing clinical observations retrospectively and anonymously.

Patients were selected in accordance with the Kawasaki disease criteria defined by the American Heart Association (AHA) in 2004 and revised in 2017, including both complete and incomplete form (Annex 2).[16]

Patient characteristics were described as numbers and percentages for categorical variables and median with interquartile ranges (IQR) for quantitative variables. Statistical analysis was performed by Microsoft Excel software.

The abnormalities of the biological examinations were established according to the laboratory standards where the assessment was carried out.

Confirmation of SARS-CoV-2 infection in patients was performed by.

- A molecular test for detecting viral RNA using a real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swabs.
- Serological tests to detect the presence of antibodies specific to SARS-CoV-2 IgM and / or IgG in the blood / serum of the patients. two types of tests were conducted depending on the availability:

1- Lateral flow chromatographic immunoassay (Abbott PANBIO ™ COVID-19 Ag RAPID TEST DEVICE) for 3 patients.
2- ELISA test (enzyme linked immunosorbent assay) for 13 patients.

Positivity for IgM or IgG, or both, was considered consistent with a previous or current infection with SARS-CoV-2.

For the therapeutic protocol used.

- Intravenous immune-globulins (IVIG) were administered at a dosage of 2 g / kg of body weight in a single dose over 12 hours.
- Acetylsalicylic acid was administered in anti-inflammatory doses (80 -100 mg / kg / day) upon admission of the patients and was maintained until thermal defervescence with regression of the biological inflammatory syndrome, then continued in anti-aggregating doses (3 to 5 mg / kg / day) for 12 weeks.
- Corticosteroid therapy based on intravenous methylprednisolone in bolus for 1 to 3 days at a dose of 30 mg / kg / day was administered in the event of macrophage activation syndrome and in the event of cardiac involvement (myocarditis and significant aneurysm).
- Immunoglobulin resistance was defined as: a persistence of fever 36 hours after the end of the IVIG infusion. In this case, a second dose of immunoglobulins was given. The treatment response was defined as a resolution of clinical signs and inflammatory markers.

RESULTS

Clinical features

As shown in table I, 16 clinical observations were collected during the period from November 26th, 2020 to February 24th, 2021. Patients were 2.5 to 15 years of age with a median age of 6.5 years, and with a predominance of male (10G / 6F): sex ratio = 1.6. Prolonged fever (> 5 days) has been reported in all patients with an average consultation time of 8 days.

Contact with a confirmed COVID-19 case was reported in 2 cases with an interval of 3-5 weeks, while a recent confirmed COVID-19 infection was reported in a single patient, with a 4-week interval. All patients had no significant medical history. Arterial hypotension was reported in one case, while oxygen desaturation was less than 92% in another; However, the remaining patients had reassuring hemodynamic and respiratory variables. The clinical presentation of Kawasaki disease was incomplete in 69% of cases (11 patients), while it was complete in 5 patients. Mucocutaneous involvement has been reported in all patients. Extremities changes were noted in 31% of cases (5 patients) and cervical lymphadenopathy in 50% of cases. Digestive signs were reported in 69% of cases, while respiratory symptoms such as cough and rhinorrhea were reported in 4 patients, among which, one case with respiratory distress and desaturation, and one case of dyspnea with chest pain.

Table I: Clinical characteristics of patients.

Clinical characteristics	Number (%)
Age (years) Median (range)	6,5 (2,5 -15)
Gender: Male Female	 10 (63) 6 (38)
Kawasaki disease presentation: Complete Incomplete	 5 (31) 11 (69)
Lips and oral cavity changes: Cheilitis Pharyngitis Glossitis	 15 (94) 11 (69) 4 (25)
Skin rash: maculopapular rash Urticaria Erythema multiforme	9 (56) 6 (38) 2 (13) 1 (6)
Changes to extremities: Palmar erythema Palmar-plantar erythema swelling of the dorsal hands and feet	5 (31) 2 (13) 2 (13) 2 (13)
Bilateral bulbar conjunctival injection	12 (75)
Cervical lymphadenopathy	8 (50)
Digestive signs:	11 (69)

Abdominal pain Diarrhea Vomits	6 (38) 6 (38) 4 (25)
Respiratory signs: Cough Rhinorrhea Dyspnea	4 (25) 4 (25) 1 (6) 2 (13)
Chest pain	2 (13)
Joint signs: Arthralgia Arthritis	3 (19) 3 (19) 1 (6)
Headache	2 (13)
Cervicalgia	1 (6)

Laboratory findings

Biologically, an inflammatory syndrome was marked in all patients with accelerated Erythrocyte sedimentation rate (ESR) and elevated C-reactive protein (CRP), ranging from 97 to 364 mg / l. Microcytic hypochromic anemia (inflammatory) was found in 2 patients (13% of cases). Leukocytosis with a predominance of neutrophils was noted in 4 patients, while lymphopenia was reported in 63% of cases (10 patients), it varied between 610 and 1500 / mm3 eosinopenia was described in 5 patients, it was 0 to 20 / mm3. Thrombocytosis was noted in 3 patients, while thrombocytopenia was noted in 2 others. More than two-thirds of the patients (75%) had hyponatremia ranging from 119 to 130 meq/L, with high levels of fibrinogen, D-dimer and hyperferritinemia. Hypertriglyceridemia was found in 44% of cases (7 patients) with two cases of hepatic cytolysis predominantly in ASAT (Aspartate aminotransferase) and one case of renal failure (table II). otherwise, a macrophage activation syndrome was identified in 3 patients. Cytobacteriological examination of the urine was requested in 13 cases (81%) and revealed aseptic leukocyturia in 6 patients. Blood culture test was performed in 10 patients (63%) and was negative for all of them. Lumbar puncture was performed in 4 patients and was also negative for all of them.

Table II: Laboratory findings of patients.

Laboratory Finding	Median (range)
Leukocyte count, x 10^9/L	112 (3,8-20,6)
Neutrophil count 10^9/L	9,3 (2,4-16,4)
Lymphocyte count, x 10^9/L	1,5 (0,61-5,8)
Eosinophils count, x 10^9/L	0,15 (0-0,61)
Hemoglobin level, g/dl	11 (8,7-14)
Platelet count, x 10^9/L	208 (102-776)
C-reactive protein level, mg/L	179 (97-364)
Erythrocyte sedimentation rate, mm/h	64 (17-125)
Serum ferritin, ng/mL	450 (90-2500)
Sodium level, mmol/L	129 (119-138)
Urea level, g/L	0,2 (0,18-1,09)
Creatinine level, mg/L	5 (3-19,7)
Alanine aminotransferase level, U/L	26 (19-57)
Aspartate aminotransferase level, U/L	30 (13-148)
Triglycerides level, g/L	2 (0,75-5,93)
D-dimer, µg/mL	4 (0,7-43,7)
Fibrinogen, g/L	5 (3,6-12)

SARS-CoV-2 test results

The table III below show that the SARS-CoV-2 real-time PCR nasal swab test performed on all of patients was negative, while the SARS-CoV-2 serology was positive in 94% of cases (15 patients).

Table III: SARS-CoV-2 Test Results.

Detection of SARS-COV-2	Number (%)
RT-PCR Negative Positive	 16 (100) 0
Positive serology IgG+, IgM+ IgG+, IgM- IgG-, IgM+ IgG-, IgM-	15 (94) 3 (19) 10 (63) 1 (6) 1 (6)
SRAS-CoV-2 = severe acute respiratory syndrome coronavirus 2, RT-PCR = reverse transcription polymerase chain reaction, IgM = immunoglobulin M, IgG = immunoglobulin G	

Imaging Findings

Table IV presents the radiographic features of the 16 patients admitted with a diagnosis of Kawasaki disease. Echocardiography was abnormal in 6 (38%) patients after a median of 9 (range 7 - 18 days) days of fever and which consisted of coronary aneurysms in 5 patients with coronary parietal thickening in 3 cases and myocarditis in 3 others. Chest imaging consistent with SAR-SCoV-2 infection has been reported in one case.

Tableau IV: Radiographic features of patients.

Radiographic features	Number (%)
Echocardiography Normal Coronary involvement Coronary artery aneurysm/ dilation Coronary vessel parietal thickening Myocarditis	 11 (69) 5 (31) 5 (31) 3 (19) 3 (19)
Chest radiography Bronchial syndrome Cardiomegaly Isolated blunting of the Costophrenic angle	11(69) 5 (31) 1 (6) 1 (6)
Chest computed tomography Ground glass opacity Pachypleuritis	3 (19) 1 (6) 1 (6)
Abdominal ultrasound Mesenteric adenolymphitis Peritoneal and pelvic effusion	4 (25) 1 (6) 2 (13)

Therapeutic management and outcomes

Acetylsalicylic acid was prescribed for all patients upon admission at an anti-inflammatory dose in 94% of cases, then at an anti-aggregating dose. Intravenous immunoglobulins were administered to 14 patients according to the single dose schedule. Furthermore, the administration of a second course of immunoglobulins was necessary in one patient. Corticosteroid therapy was given as a bolus of methylprednisolone for 3 days in 4 patients, and as a single bolus in another (table V). The evolution was favorable for all patients with obtaining apyrexia and resolution of the mucocutaneous manifestations within 24 hours after the administration of IVIG in 81% of cases and reduction of the inflammatory syndrome in all patients before their discharge with an average hospital stay of 7 days. No thrombotic or embolic event was observed. There were no deaths within patients.

Table V: treatments administered to patients.

Treatments received	Number (%)
Acetylsalicylic acid	
Anti-inflammatory dose (80-100 mg/Kg)	15 (94)
Anti-aggregant dose (3-5mg/Kg)	15 (94)
Intravenous immunoglobulin (IVIG)	
Single infusion	15 (94)
Second infusion	1 (6)
bolus of corticosteroids:	5 (31)
for 3 days	4 (25)
for 1 day	1 (6)
Other therapies:	
Antibiotic therapy	6 (38)
Ceftriaxion	3 (19)
Macrolide	3 (19)
Antihistamines	1 (6)
Digoxin	1 (6)
Enoxaparin sodium	2 (13)
Furosemide	2 (13)

Annexes

Annex 1

World Health Organization case definition of MIS-C[13]	Children and adolescents 0 to 19 years of age with: Fever> 3 days AND at least two of the following signs: Skin rash, or bilateral non-purulent conjunctivitis, or mucocutaneous inflammation signs (cheilitis, edema of the hands or feet) Hypotension or shock Features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (echocardiographic abnormalities or elevated troponin / NT-proBNP levels) Evidence of coagulopathy (PT defect, APTT, elevated D-dimers) Acute gastrointestinal complaints (diarrhea, vomiting or abdominal pain) AND Elevated inflammatory markers such as C-reactive protein, procalcitonin or erythrocyte sedimentation rate AND No other obvious microbial cause of inflammation, such as bacterial sepsis or staphylococcal or streptococcal shock syndromes AND Evidence of a COVID-19 infection (RT-PCR, antigen test or positive serology) or likely contact with patients with COVID-19
Centers for Disease Control and Prevention case definition of MIS-C[14]	An individual aged <21 years presenting with Clinical criteria: Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h AND Evidence of clinically severe illness requiring hospitalization Multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Biological inflammation, with one or more abnormalities: An elevated C-reactive protein level, procalcitonin, erythrocyte sedimentation rate, fibrinogen, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6); elevated neutrophils; reduced lymphocytes; and low albumin. AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Royal College of Pediatrics and Child Health case definition of MIS-C[15]	A child (age not specified) with. Clinical criteria: persistent fever > 38,5 °C and, evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) This may include children fulfilling full or partial criteria for Kawasaki disease. Biological inflammation, with: Neutrophilia, elevated C-reactive protein level and lymphopaenia. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice). SARS-CoV-2 PCR testing may be positive or negative.
Abbreviations: MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PT, prothrombin time; APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.	

Annex 2

Diagnostic criteria for Kawasaki disease[16]
Classic Kawasaki disease. fever of five days or more with at least four of five features: bilateral conjunctival injection oral changes such as cracked and erythematous lips and strawberry tongue Polymorphic rash Changes in extremities (acute: peripheral edema of hands and feet, erythema of palms and soles; subactue: periungual peeling of fingers and toes Cervical lymphadenopathy (usually unilateral and >1,5 cm in diameter Atypical or incomplete Kawasaki disease: fever of five days or more with two or three of the features.

DISCUSSION

Since the start of the COVID-19 pandemic, numerous cases of inflammatory disease with multi-organ syndrome reminiscent of Kawasaki disease (KD) have been reported in the pediatric population.[10,12,17-21]

The first case of Kawasaki disease in a person with confirmed COVID-19 was published on April 7th, 2020.It was a 6-month-old infant with fever, mild respiratory symptoms and classic symptoms of Kawasaki disease.[22] Then, a public health alert was issued to doctors on April 25th, 2020 by the National Health Service (NHS) of the United Kingdom, to inform them about the emergence of a severe disease, affecting the majority of children who were tested positive for the COVID-19. This new has similar characteristics to atypical Kawasaki disease and toxic shock syndrome, with laboratory abnormalities reminiscent of those seen in children with severe COVID-19. Digestive symptoms as well as severe heart damage were also common manifestations of this disease. Soon after, Verdoni et al.[10] confirmed these data through the cohort published by the Lancet reporting an increase in the incidence of Kawasaki disease (30 times more) during the SARS-CoV-2 epidemic; he also confirmed that the disease was much more severe, and these patients were older than those with usual Kawasaki disease. After these first alerts were issued, other sets of cases began to submerge in countries in Europe and North America, but no cases of MIS-C were initially reported in Asian countries where the COVID-19 pandemic began, and the incidence of KD is generally higher.[23]

This new entity, called MIS-C (or PISM), can occur either during the infectious period of SARS-CoV-2 or post-infection. Indeed, by observing the epidemic curve of this inflammatory syndrome related to COVID-19 in the most affected countries, we noticed that the peak of this emerging disease occurred 4 to 6 weeks after the peak of the COVID-19 epidemic, that is to say, when the number of new COVID-19 cases has decreased, which suggests an immune response, or rather a delayed complication of the virus.[10,12,18,20,24-26]

Moreover, the absence of the virus in the respiratory tract in the majority of the published case series in which the diagnosis of a previous infection with SARS-CoV-2 has been confirmed by serological tests also confirms this hypothesis.[18,24] Nevertheless, in some cases, the two diseases could be contemporaneous[10], hence the interest of performing both RT-PCR and SARS-CoV-2 serology in patients meeting MIS-C criteria. In this series of cases, the RT-PCR testing for SARS-CoV-2 was negative for all patients. Among the 16 identified cases, 15 had a positive SARS-CoV-2 serology, including 3

patients with positive IgG and IgM and one patient with positive IgM and negative IgG, while one patient had a negative result for both. Indeed, a negative serology in a patient fulfilling the diagnostic criteria of MIS-C cannot exclude an infection by this virus because it seems that IgG antibodies against SARS-CoV-2 can disappear quickly, especially in asymptomatic people.[27]

MIS-C can affect all pediatric age groups; However, analysis of different studies showed that the median age of patients was around 8 years[10,17-21,24], while it was 6.5 years in the studied series. The male sex predominated in 63% of cases with a ratio = 1.6, thus joining the data literature where a male predominance was reported in approximately 61% of cases.[17,21,25,28-30] This male predominance is also described in the usual KD. The average deadline for consultation reported in our series was 8 days, more delayed than what was reported in the other series (4 to 5 days).[19,31]

Persistent fever is a common feature in all published cases of MIS-C. Gastrointestinal manifestations have been frequently described, including diarrhea, vomiting or abdominal pain which may in some cases mimic an acute surgical abdomen, while respiratory symptoms are less frequent, thus joining the results of our cases. Indeed, SARS-CoV-2 penetrates into the host cell by binding of the S protein to the ACE2 receptor. This entry is facilitated by cleavage of the protein S by membrane proteases such as TMPRSS2.[32,33] Recent studies have shown that adults have greater expressions of the ACE2 receptor and TMPRSS2 protease on alveolar mucosal cells compared to children.[34] This explains why children have fewer respiratory complications after SARS-CoV-2. Among the other main clinical features in these patients with MIS-C, we find the mucocutaneous symptoms which are also very common, and reminiscent of KD (non-purulent conjunctivitis, cheilitis, rash, erythema or edema of the hands or feet). These mucocutaneous manifestations have been reported in all patients. although, it is possible that the clinical presentation of these patients does not meet all the classic criteria of KD as it was the case in the conducted series, where the clinical presentation was incomplete in 69% of cases (11 patients). Indeed, the literature data indicate that the prevalence of the incomplete form of Kawasaki disease, which would be from 15% to 36.2%[35,36], significantly increased during this COVID-19 pandemic to reach a rate of 45.9%, but which may differ depending on the region.[37] As well as only 25% to 50% of the cases of MIS-C reported in the literature fulfilled all the diagnostic criteria for KD.[10,18,20,21,24,26], which should encourage pediatricians to be vigilant and aware of this atypical presentation of COVID-19, thus allowing early diagnosis and adequate therapeutic management.

Biologically, patients with MIS-C have a greater inflammatory syndrome than that usually described in Kawasaki disease, with an elevated level of markers such as ESR, CRP, procalcitonin and ferritinemia. There is also lymphopenia in opposition to the neutrophilic polynucleosis described in Kawasaki disease, a lower platelet count, deeper anemia and more severe hyponatremia, with an elevated fibrinogen and D-dimer level.[18,21,25] This indicates the existence of an inflammatory process superior to the one encountered in classic Kawasaki disease, and similar to the one encountered during the cytokine storm in adult patients infected with SARS-CoV-2.[38] These significant abnormalities in haemostasis suggest a high risk of thrombosis; However, clinical thromboembolic events in patients with MIS-C have not been described by various pediatric studies. Eosinopenia was detected in 5 cases (33%), including 2 patients with cardiac involvement such as myocarditis and aneurysm coronary artery disease, thus contrasting with eosinophilia described in patients developing coronary aneurysm during Kawasaki disease.[39] Nevertheless, this eosinopenia has been reported to be characteristic of patients with severe forms of COVID-19, in addition to other biomarkers, such as lymphopenia.[40,41] and hyponatremia.[42]

Cardiovascular involvement is one of the most serious complications in patients with MIS-C. Cardiac biomarkers including troponin and especially NT-pro-BNP levels are extremely high compared to those described in patients with usual KD.[43] According to various studies, 50% of children with MIS-C were presented in a state of cardiogenic shock.[10,18,19,21,28] and 40% to 80% of cases with myocarditis.[10,19,20,24], unlike the Classic KD, where their frequency does not exceed 5%.[44] In our series, myocardial involvement was described in approximately 20% of cases (3 patients). Coronary anomalies were reported in 9 to 24% of patients with MIS-C[18-21] and they were most often in the form of small aneurysms or dilation, which was the case in our series where coronary aneurysms were present in 31% of cases, while coronary wall thickening was reported in 19% of cases. Other less common heart attacks have been reported such as pericarditis, and cardiac arrhythmia.[19,20]

The therapeutic management of these patients with MIS-C is often adapted to the one of Kawasaki disease given the similarities between the two conditions. However, the American College of Rheumatology (ACR) recently published guidelines for the treatment of MIS-C[45], recommending the use as first-line therapy of immunoglobulins (IVIG) and / or high dose of corticosteroids. In contrast, some authors have reported better therapeutic efficacy in children treated with this combination, compared to those who received IVIG only.[24,46] According to the different published case series, approximately 30% to 80% of patients are at risk of not responding to IVIG alone and may require corticosteroid therapy or adjunct immunomodulatory therapy (ex: anakinra) to control inflammation[10,18-20], unlike classical KD where resistance to IVIG is only observed in less than 15% of cases.[47] The dose of corticosteroids is the same as that recommended for

severe Kawasaki disease[48] and is administered intravenously as a bolus of methylprednisolone at 10 to 30 mg / kg / day for 3 to 7 days. Acetylsalicylic acid (ASA) in anti-inflammatory doses (80-100 mg / kg / day)[19] is classically associated with this treatment with immunoglobulins (IVIG) and / or corticosteroids as in KD.[16] According to ACR recommendations, acetylsalicylic acid in antiaggregating doses (3 to 5 mg / kg / day up to 81 mg, once daily) should be continued in patients with MIS-C and without risk of bleeding, until the platelet count returns to normal and confirmation of the absence of coronary artery disease beyond 4 weeks from diagnosis.[45] In addition, thromboprophylaxis will be recommended in high-risk situations. If first-line treatment fails, a second dose of IVIG or adjuvant therapies such as anakinra (anti-IL-1), infliximab (a TNF-alpha inhibitor) or tocilizumab (anti-IL-1) IL-6) could also be considered.[18,21,24,49] In any case, these different therapies must be adapted according to each patient.

limitations of this study

As a case series and in view of the small number of patients, this study does not allow in-depth comparisons of the different characteristics of this disease with adequate statistical power, nor to provide evidence on the effectiveness of the treatment of MIS-C. As a result, other studies with a larger group of cases will be necessary in order to better understand this new entity, which is MIS-C and whose pathophysiology remains poorly understood until now.

CONCLUSIONS

Multisystem inflammatory syndrome (MIS-C) appears to result from a delayed immune response to infection with SARS-COV-2. Furthermore, the existence of clinical similarity between Kawasaki disease and MIS-C may suggest an underlying genetic predisposition; however, the absence of reported cases in Asia, where the incidence of KD is higher, implies the need of in-depth genetic studies. Clinicians should suspect MIS-C in any child with high fever and unexplained biological inflammatory syndrome in this pandemic context, in order to initiate early treatment and adequate management. Therefore, countries where SARS-CoV-2 has spread may face a shortage of supply of intravenous immunoglobulins due to the increasing number of these cases of MIS-C and will, however, need to anticipate this situation. Finally, although the overall mortality in these patients remains low, medium and long-term monitoring should be adopted to detect possible complications, in particular cardiac origins that may appear later.

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