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ORIGINAL ARTICLE

Pediatric inflammatory multisystem syndrome (PIMS) temporally related to SARS-CoV-2

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Abstract

The first case report of a child, a 6-month-old female infant, with Kawasaki disease (KD) and concurrent COVID-19 was published in the United States on 7 April 2020. Since this first report, countries with outbreaks of SARS-CoV-2 have reported further cases of pediatric inflammatory multisystem syndrome temporally related to SARS-CoV-2 (MIS-C). This syndrome overlaps clinical and laboratorial features of Kawasaki disease (typical or incomplete), staphylococcal and streptococcal toxic shock syndromes, bacterial sepsis and macrophage activation syndrome. This syndrome usually affects mostly children older than 5 years of age, predominantly afro descendent in most studies, and has a higher incidence of cardiac manifestations. A possible temporal association with SARS-COV-2 infection has been hypothesized because some of the children were positive for SARS-CoV-2 either by polymerase chain reaction (RT-PCR) or serology. Those children had prolonged high fever, rash, and prominent gastrointestinal symptoms in 50-60% of the cases (abdominal pain, non-bloody diarrhea, ascites and ileitis), conjunctivitis, lymphadenopathy, irritability and headache. Some severe cases, presented with shock resulting from cardiac dysfunction, with or without myocarditis, or coronary artery aneurysm. Respiratory symptoms could be present, usually correlated with concurrent shock. In this article, we describe definitions, clinical and laboratorial findings of this intriguing syndrome to alert pediatricians and to guide with respect to diagnosis and management of these patients.

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What is Kawasaki Disease and how is it diagnosed?

Kawasaki's disease (KD) is a primary acute systemic vasculitis, with a predominant involvement of medium-caliber vessels, the etiology of which has not been fully elucidated. It represents the main cause of heart disease acquired in childhood in developed countries and 5% of acute coronary syndromes in adults under 40 years of age. Coronary artery aneurysms are known to occur in about 25% of untreated or incorrectly treated cases. Thus, it is up to the pediatrician to establish the diagnosis and institute early therapeutic measures¹. Therefore, in 2004, the American Heart Association (AHA) published guidelines for its diagnosis, treatment and long-term follow-up. In 2017, the document was revised and updated, incorporating new evidence and algorithms in relation to its clinical management².

The classical clinical picture of KD is based on the mandatory presence of fever for at least 5 days associated with at least 4 of the 5 criteria established by the AHA; they are alteration of lips and oral cavity, conjunctival hyperemia, alterations of extremities, polymorph and cervical lymphadenopathy ≥ 1.5 cm, usually unilateral². In this way, its diagnosis is primarily clinical and it is necessary to have a thorough medical care that includes a well-done history and a detailed physical examination. Fever is usually high and continuous, around 39°C to 40°C. If proper treatment is not instituted, it can last for 1 to 3 weeks. Lip and oral changes include erythema, dryness, fissures and lip bleeding. Diffuse hyperemia of the oropharyngeal mucosa and "raspberry or strawberry tongue" may also be present. Among conjunctival changes, the most common is bilateral non-exudative bulbar conjunctivitis, which in most cases begins shortly after fever. Anterior uveitis can be seen on an eye exam during the first few days of fever. The changes in the extremities are diverse and include palmo-plantar erythema, painful swelling of the back of the hands and feet and periungueal desquamation, which can become diffuse within 2 to 3 weeks of the onset of fever. The rashes appear around the fifth day of fever, being of the non-vesicular polymorph rash type. Cervical lymphadenopathy is the least common clinical manifestation. It is usually unilateral, ≥ 1.5 cm in size, located in the anterior cervical triangle. In the convalescence phase, Beau lines can be observed, which consist of deep transverse grooves in the nails and alopecia¹⁻³.

KD should be considered in any child with unexplained and prolonged fever. In the presence of less than four clinical criteria or an echocardiogram compatible with coronary dilation/aneurysm, incomplete KD should always be considered. In these cases, the diagnosis can be made if there are 3 or more of the following laboratory changes: erythrocyte sedimentation rate (ESR) > 40 mm/1st hour, C-reactive protein (CRP) > 3 mg/dL; platelets $> 450,000/\text{mm}^3$ (after 7 days of illness); anemia for age; leukocytosis $> 15,000/\text{mm}^3$; TGP > 50 U/L; albumin < 3 g/dL; sterile pyuria; hyponatremia;

and coronary dimensions by means of the Z-score > 2.5 on echocardiography^{2,3}. Severe cases of KD may present as toxic shock syndrome, defined as sustained systolic hypotension (lowering blood pressure above 20% from baseline) or clinical signs of poor perfusion, being a potentially fatal complication of KD and which can be accompanied by multiple organ dysfunction syndrome⁴.

What is the cytokine storm/release syndrome?

The cytokine storm/release syndrome (cytokine storm) is a hyper-inflammatory, multisystemic and potentially lethal syndrome if not treated early, included in the spectrum of Hemophagocytic Lympho-Histiocytosis (HLH). It is caused by uncontrolled activation of cytotoxic T cells, with consequent massive release of pro-inflammatory mediators (interleukins 1, 6, 18, tumor necrosis factor and γ -interferon)⁵. The affected organs (e.g. bone marrow, liver) have a buildup of macrophages that cause phagocytosis, dysfunction and amplify the activation of more cells and release of more cytokines⁶.

HLH can be triggered by infectious causes (mainly viruses of the herpes virus group, e.g. Epstein-Barr, cytomegalovirus) and non-infectious ones, such as neoplasms, post-transplantation, autoimmune diseases, primary immunodeficiencies, drugs (chemotherapy, phenytoin, antiretroviral drugs) and biological agents, among others. When the triggering factor is present, we are faced with the secondary form of HLH. The primary form, on the other hand, occurs due to mutations in the genes responsible for some stage of the formation of cytotoxic granules and activation of T lymphocytes. The macrophage activation syndrome (MAS) is the name given to HLH secondary to rheumatological diseases, more often systemic JIA, systemic lupus erythematosus⁶. MAS can also complicate cases of KD, but there is a probable underdiagnosis of MAS, due to clinical and laboratory similarities. With the COVID pandemic¹⁹, a greater number of cases of MAS have been diagnosed in KD⁷.

Its most characteristic laboratory findings are cytopenia (absolute or relative), hyperferritinemia, increased transaminases, hypertriglyceridemia, decreased fibrinogen, decreased ESR and increased CRP.

What are the main clinical manifestations of MIS-C?

The first case report of a child, a 6-month-old infant, with concomitant KD and COVID-19 was published in the United States on April 7, 2020⁸. Since then, case reports and case series have been published in other countries. European countries (United Kingdom, Italy, Spain, France, Switzerland), United States and Latin America, of a severe multisystemic inflammatory syndrome, which shares clinical and laboratory characteristics with KD (either typical or incomplete), toxic shock syndrome - staphylococcal or streptococcal, bacterial sepsis and macrophage activation syndrome²⁻⁷. But, it also

shows significant differences, such as, for example, the preferential involvement of children over 5 years of age, higher rates of cardiac involvement (myocarditis, valvulitis, pericarditis, coronary abnormalities) and the predominance of Afro-descendant ethnicity in most studies⁹⁻¹⁴.

These cases occurred days or weeks after COVID-19, suggesting a possible temporal association with SARS-CoV-2 infection, because some of these children were positive for SARS-CoV-2 by polymerase chain reaction (PCR) or serology. This syndrome received the name of MIS-C or PIMS-TS^{4,15}. According to media reports, medical society alert notes and scientific publications, as of June 20, 2020, more than 300 suspected cases of MIS-C are currently under investigation. These patients had persistent high fever, exuberant gastrointestinal manifestations in 50-60% of cases (severe abdominal pain, diarrhea, vomiting), non-purulent conjunctivitis, polymorphic rash, hand and foot edema, oral mucositis, generalized lymphadenopathy (including mediastinal and intra-abdominal), hepatosplenomegaly, serositis (pleuritis, pericarditis, ascites), irritability, headache, altered level of consciousness⁴⁻¹⁵. Some cases were complicated by shock (arterial hypotension, tachycardia, perfusion disorder), resulting both from myocardial dysfunction and decreased peripheral vascular resistance, usually requiring resuscitation with crystalloids and in some cases infusion of vasoactive amines. Respiratory symptoms are usually less frequent and relevant, and may even be caused by hemodynamic decompensation^{16,17}.

Some authors provisionally suggest the existence of three disease patterns among children hospitalized with MIS-C. A group of children has persistent fever and a significant increase in evidence of inflammatory activity, but without characteristics of KD, shock or organ failure. A second group meets the diagnostic criteria for KD. In addition, a third group presents severe disease with myocardial dysfunction, shock and coronary aneurysms, in addition to a wide spectrum of manifestations including fever, gastrointestinal symptoms and rash¹⁸.

What are the exams that I request on suspicion of MIS-C?

In the presence of a child/adolescent with signs and symptoms suggestive of MIS-C, a series of tests should be carried out to investigate the involvement of various organs/systems and to monitor the inflammatory activity and the possibility of the state of hypercoagulability. To investigate the infection by SARS-CoV-2, RT-PCR, serology IgG and IgM) or antigen search^{19,20} can be performed. The absence of positive tests for evidence of infection by SARS-CoV-2 does not invalidate the diagnostic suspicion, and the epidemiological history is considered^{12,21}.

In the initial approach, it is important to carry out the tests for inflammatory activity (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]), complete blood count for the

assessment of hematometry changes, of the white series and platelets, assessment of renal function (urea creatinine), liver function and bile ducts (AST, ALT, total proteins and albumin, alkaline phosphatase, γ -GT, total bilirubin and fractions), blood glucose, electrolytes (sodium and potassium)^{13,21}.

The search for other possible infectious causes for the presented condition should be done with urine tests (EAS, urine culture), co-culture, ASLO, oropharynx culture, blood culture, serology for other viral infections, lumbar puncture for CSF analysis when there are signs of involvement of the central nervous system, preceded or not by imaging (computed tomography)¹⁸. In patients with respiratory symptoms, performing a viral panel to search for other viruses can help in the differential diagnosis. In these cases, arterial blood gas analysis, chest radiography, chest ultrasound or chest tomography are also recommended depending on the clinical signs and symptoms^{12,20}.

When the initial suspicion is confirmed, the assessment should be completed with the request for LDH, triglycerides, ferritin, CK, investigation of coagulation disorders with the measurement of TAP, PTT, D-dimer, fibrinogen, myocardial function markers (troponin, CK-mb, myoglobin, pro-BNP) and tests to assess the possibility of various cardiovascular manifestations with electrocardiogram, echocardiogram and chest radiography^{19,20}.

Cardiac computed tomography may be necessary in cases with suspected distal coronary aneurysm, in which evaluation by echocardiography is difficult and some algorithms suggest that all patients who present cardiac dysfunction, even if transitory, undergo cardiac magnetic resonance after 2-6 months of evolution¹⁹.

In cases of gastrointestinal system involvement, abdominal imaging tests such as radiography, ultrasound and computed tomography may be necessary to assess complications such as hepatosplenomegaly, vesicular hydrops, serositis, adenitis, colitis, among others. When available, procalcitonin and a cytokine panel should be requested to monitor the inflammatory condition^{19,20}.

How do I suspect that a child has “multisystem inflammatory syndrome” (MIS-C)?

The pediatrician should be attentive to the diagnosis of MIS-C in every child or adolescent who has persistent fever, evidence of inflammatory activity with involvement of one or more organs (cardiac, renal, respiratory, gastrointestinal or neurological), after exclusion of infectious causes that may justify the condition. Diagnostic confirmation of SARS-CoV-2 infection is not mandatory, and may only have a history of exposure to the virus¹⁹⁻²³.

The criteria established so far for the diagnosis of MIS-C are from the Centers for Disease Control (CDC) and the World Health Organization (WHO), with minor differences, which may assist pediatricians in diagnosing this clinical condition^{12,13}.

Centers for Disease Control (CDC, USA)	World Health Organization (WHO)
Age < 21 years	Age: 0-19 years
Fever >38°C or subjective, for ≥24h	Fever for ≥3 days
+	+
Inflammation laboratory (1 or more of the following tests: C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, interleukin 6 (IL-6), neutrophilia, lymphopenia and hypoalbuminemia.	Inflammation laboratory (erythrocyte sedimentation rate, C-reactive protein or procalcitonin)
+	+
Evidence of serious clinical illness, requiring hospitalization, with multisystemic involvement (≥2 organs):	At least 2 of the following changes:
• Cardiac (e.g., shock, elevated troponin, pro-BNP, echocardiographic changes, arrhythmias); • Renal (e.g., acute kidney injury or kidney failure); • Respiratory (e.g. pneumonia, acute respiratory distress syndrome, pulmonary embolism); • Hematological (ex: high D-dimer, thrombophilia, thrombocytopenia). • Gastrointestinal (e.g., elevated bilirubin, liver enzymes or diarrhea); • Neurological (e.g., stroke, aseptic meningitis, encephalopathy).	• Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammatory signs (oral cavity, hands or feet); • Hypotension or shock; • Findings of myocardial dysfunction, pericarditis, valvulitis or coronary changes (echocardiographic or troponin elevation or NT-pro-BNP); • Evidence of coagulopathy (TAP, PTT and D-dimer). • Acute gastrointestinal symptoms (diarrhea, vomiting or abdominal pain)
+	+
Without another plausible diagnosis.	No other evident microbiological cause of inflammation, including bacterial sepsis, staphylococcal and streptococcal toxic shock syndrome
+	+
Positive test for SARS-CoV-2 by RT-PCR, serology, OR antigen OR history of exposure in the last 4 weeks of symptom onset.	Evidence of COVID-19 (RT-PCR, antigen or serology) OR likely contact with patients with COVID

Adapted from references 12 and 13.

How do I treat MIS-C?

There is no validated protocol for the treatment of MIS-C and each service in different parts of the world has been conducting similar, although not always the same, based on the clinical condition expressed in each patient and their severity. In cases presenting with diagnostic criteria for classical KD, usual therapy with intravenous gamma globulin (IVIG) and acetylsalicylic acid (aspirin)² has been indicated.

IVIG should be prescribed at a dose of 2g/kg with prolonged infusion over 10-12 hours. It can be divided into 2 or more days, depending on the patient's hemodynamic conditions.

Aspirin can be used at a dose of 80-100 mg/kg/day as a non-steroidal anti-inflammatory initially, changing to a dose of 3-5 mg/kg/day (anti-platelet aggregation dose) after fever abatement². Many services recommend a lower initial dose of aspirin, 30-50 mg/kg/day, while others recommend the dose of 3-5 mg/kg/day from the beginning, since there seems to be no change in evolution and prognosis of children with Kawasaki disease with low, moderate or high dose of the drug²⁴.

In cases of incomplete KD, it is a good idea to treat it the same way. Many services have indicated IVIG for MIS-C even in cases that do not meet criteria for KD, since it is also very useful for cases of sepsis and for situations with significant increases in cytokine release, such as MAS and severe cases of MIS- C. In recent cases of KD that appear to be temporarily associated with the SARS-CoV-2 virus, cardiac involvement with severe myocardial dysfunction has been seen, which are described, but are not usually found in classical KD. In cases of severe myocardial dysfunction in KD that meet criteria for MIS-C, the treatment should be more comprehensive, as we will see below²⁵⁻²⁶.

The treatment of MIS-C deserves special considerations. Whenever they fulfill criteria for complete or incomplete KD, the treatment mentioned above must be started. Many patients come to the hospital in severe conditions, hypotensive, with peripheral vasoplegia and dehydrated. Immediate hydroelectrolytic replacement should be performed and, at least while there is no certainty of the diagnosis and due to the similarity with sepsis, antibiotic therapy should be

initiated. In most cases, the use of inotropic drugs is necessary and these patients should generally be admitted to intensive care units^{22,23}.

In mild cases of MIS-C (minimal damage to any organ, without the need for respiratory support), the indication for initial support therapy, which may change depending on the worsening of clinical evolution, is often sufficient for patients. Consider the use of corticosteroids in the presence of myocardial involvement, even if minimal. In mild cases, a dose of 2 mg/kg/day of methylprednisolone divided 3 to 4 times can be indicated, with a progressive reduction in 2-3 weeks (2mg/kg/day → 1mg/kg/day → 0.5mg/kg/day)^{25,26}.

Moderate cases of MIS-C (mildly injured one or more organs and need for some type of respiratory support) and severe (moderate or severe damage to several organs, hypotension, respiratory failure, ventricular dysfunction) should be managed, as described above, with IVIG and aspirin, and with intravenous corticosteroids. For the most severe cases, methylprednisolone as a pulse therapy at a dose of 30 mg/kg/day for 3 days is recommended, and in moderate cases 10-20 mg/kg/day for 1-3 days. In both cases, a maintenance dose of 2 mg/kg/day should be prescribed after the pulse therapy. Cases refractory to two doses of IVIG and corticosteroids may require biological agents (anti IL-1, anti IL-6 or anti-TNF) because, in these cases, an exacerbated release of cytokines (cytokine storm) must be occurring. The use of anticoagulation in these patients is still controversial. They have a greater tendency to present thromboembolic phenomena and the dosage of D-dimer is usually very high. Mild to moderate cases of MIS-C can be managed with a prophylactic dose of enoxaparin and, in more severe cases, a therapeutic dose, although there is no consensus on its use²⁵. Anticoagulation should be assessed individually, taking into account the risk of bleeding.

The clinical evolution of early treated patients has been favorable. The recovery of left ventricular function is very common and occurs within a few days of treatment.²⁶

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