Multisystem inflammatory syndrome associated with COVID19 in children and adolescents: calling for diagnosis

Síndrome inflamatorio multisistémico asociado a COVID-19 en niños y adolescentes: un llamado al diagnóstico*

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In December of 2019, a new virus emerged from the city of Wuhan, China and was capable to produce acute respiratory disease, ranging from mild clinical presentations to fulminant disease, especially in adults. Later identified as the SARS-CoV-2 virus[1], this is the causal agent of the current COVID-19 pandemic as declared by the World Health Organization (WHO) in March of 2020[2].

Since the beginning of the pandemic, the majority of reports of epidemiological surveillance and medical publications have documented that worldwide approximately 97-98% of all registered COVID cases occur in adults. Of the remaining percentage of cases in children, most of these will be mild or asymptomatic infections. From those children requiring admission to emergency rooms, pediatric wards or pediatric intensive care units (PICU's), most will be due to respiratory distress or pneumonia.

On April 24 2020, the Rheumatology Study Group of the Italian Society of Pediatrics issued an alert to its members and health care workers about a local increase in the number of incomplete or atypical Kawasaki disease (KD) cases with increased resistance to intravenous immunoglobulin (IVIG), tendency toward macrophage activation syndrome (MAS) and admissions to PICU's. In some of these children there was laboratory evidence of a recent SARS-CoV2 infection or household contacts that had been diagnosed with the virus. Two days later, the Paediatric Intensive Care Society and the Royal College of Paediatrics and Child Health of the United Kingdom (UK) also issued an alert statement through their social media networks and websites due to an increase of clinical presentations of overlapping atypical KD and Toxic Shock Syndrome (TSS) among children of all ages from London and other regions of the UK[3]. An interest finding among these patients, besides their hyper-inflammatory shock, was they had also severe gastrointestinal manifestations. Following these alerts, on April 28 2020 the Spanish Association of Pediatrics issued an alert to parents due to the increase of similar cases as those described in Italy and the UK[4]. After these reports, the first cases in the United States were reported, especially in New York State,[5] where until today to date the number of reports already exceeds 200 suspected cases (in press).

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On May 1st 2020, the Royal College of Paediatrics and Child Health of the United Kingdom designated this new clinical entity with the name of Paediatric Multisystem Inflammatory Syndrome (PMIS or PIMS) and proposed a case definition for a timely recognition.[6] This consisted on: 1) a child with persistent fever, inflammation and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with other findings, including partial or complete criteria for KD; 2) exclusion of any other microbial cause; 3) a SARS-CoV-2 PCR testing may be either positive or negative.

Following this definition, on May 14 the Centers for Disease Control and Prevention (CDC) modified the case definition and proposed naming it MIS-C.[7] The next day, the WHO defines this clinical entity as Multisystem Inflammatory Syndrome (MIS) in children and adolescents with COVID-19.[8] This primary case definition applies for children and adolescents aged 0 to 19 years of age fulfilling the criteria of fever ≥ 3 days

AND 2 of the following:

- Rash or bilateral non-suppurative conjunctivitis or mucocutaneous inflammation (mouth, hands or feet)
- Hypotension or shock
- Findings of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or increased troponin/ NT-proBNP levels)
- Evidence of coagulopathy (by PT, PTT, elevated d-dimers)
- Acute gastrointestinal manifestations (diarrhea, vomiting, or abdominal pain)

AND

Elevated inflammation markers such as erythrosedimentation rate (ESR), C-reactive protein, or procalcitonin

AND

Absence of other microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes (STS)

AND

Evidence of COVID-19 (RT-PCR, antigen test or positive serology), or likely contact with patients with COVID-19.

The first medical publication of the first pediatric cases came from England on May 6 2020, describing the first 8 patients with MIS.[9] In this report, the authors describe an increase in the number of cases during a 10-day period in mid-April of hyperinflammatory shock, atypical KD, Kawasaki Disease Shock Syndrome (KDSS), and TSS. Unlike most children with KD, all of them were older than five years of age except for a 4-year-old. These patients had significant gastrointestinal symptoms, all progressed to refractory vasoplegic warm shock refractory to volume and required inotropic support. Among other echocardiographic findings, one patient had severe coronary dilation and another one pericoronary hyperechogenicity. All were treated with IVIG and antibiotics, and 7 of the 8 were discharged from the PICU between day four and six. A 14-year-old patient died of arrhythmia, refractory shock and a stroke. SARS-CoV2 was confirmed in two patients and in another four there was contact with positive family members.

Italy's first publication about this new syndrome came from researchers at the General Hospital of Bergamo,[10] in which the authors retrospectively compared two time periods of pediatric cases similar to KD ("Kawasaki-like"), from January 1rst 2015 to February 17th 2020, and from February 18th to April 20th 2020. In this second period, they documented 10 children with "Kawasaki-like" pictures and half of whom had a classical clinical presentation. This represented a 30-fold increase in the number of cases compared to the previous period. Comparatively, the ages of both groups were 3 (range 2-5) years versus 7.5 (range 3-5) years, and only one of the ten was under five years. In all patients, an increase in acute inflammation markers was common, but in all blood cultures were sterile. RT-PCR for SARS-CoV2 was positive in two of them, and an IgG positive was seen in 80%, compared to only 30% with positive IgM. The echocardiogram was abnormal in 6 (60%) of them, and 2 patients had coronary aneurysms greater than 4 mm. All patients were treated with IVIG, methylprednisolone as co-adjuvant therapy in eight of them, acetylsalicylic acid (ASA) in two, and inotropic in two.

A recent publication retrospectively analyzed 35 children who were hospitalized with acute left ventricular systolic dysfunction or cardiogenic shock and multisystemic inflammation[11] among 12 hospitals in France and 1 in Switzerland between March 22th and April 30th 2020. Median age was 10 years, none had underlying heart disease. SARS-CoV2 infection was documented in 31 (88.5%), and a recent contact history with family members with acute respiratory symptoms in 37%. Eighty percent had gastrointestinal symptoms and 2 of them required acute abdominal exploratory laparotomy. An 83% were admitted directly to the PICU, and 80% of patients were in cardiogenic shock and required inotropic drugs. The echocardiogram documented coronary artery dilation in 17%, but not aneurysms were seen on the first echocardiogram. There were no deaths.

The pandemic has surprised all of us, and this new hyper-inflammatory syndrome in children and adolescents is yet another proof of it. One month after its first description and with the evidence described briefly here and another being recently published,[12-14] this phenomenon seems more post-infectious and in which a cytokine storm similar to that described in adults occur, but with

a different clinical spectrum of manifestations. Increased markers of acute inflammation have been common in all reports, as well as the increase of troponin, ferritin, D dimer, and proBNP levels. Unlike classic KD cases which in 80% of patients occur in children under 5 years of age, these reports so far about MIS usually occur predominantly in school-aged children or adolescents. Current available data so far suggests that MIS shares a common pathophysiological pathway with that that described in KD, KDSS, TSS, and MAS.[15-17] It is unknown which is the best treatment of these patients because a greater number of cases and controlled clinical trials are required; but the truth is that this entity must be added to the list of causes of coronary abnormalities in infants, children and febrile adolescents.

We urgently need prospective data from multicenter networks due to the lower frequency of COVID-19 in pediatrics. To accomplish this, Latin America has different research and surveillance networks that can be extremely useful for it. In the meantime, clinicians in charge of these children and adolescents should know the diagnostic criteria of this new syndrome and be alert specially in countries with recent increasing number of COVID19 cases such as Brazil, Chile, and Ecuador, where the majority of these seriously ill cases may occur weeks after the infection by SARS-CoV2.

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