Multi-Inflammatory Syndrome in Children related to SARS-CoV-2 in Spain

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Abstract

Some clusters of children with a multisystem inflammatory syndrome associated with SARS-CoV-2 infection (MIS-C) have been reported. We describe the epidemiological and clinical features of children with MIS-C in Spain. MIS-C is a potentially severe condition that presents in children with recent SARS-CoV-2 infection.

Keywords: Multisystem inflammatory syndrome, Pediatric inflammatory multisystemic syndrome, COVID-19, SARS-CoV-2, Kawasaki disease.

Introduction

In the last weeks, some clusters of children with a multisystem inflammatory syndrome (MIS-C) linked to SARS-CoV-2 infection have been described in the United Kingdom, France, Italy and USA, among other countries.[1,2] This syndrome shares features of Kawasaki disease, toxic shock syndrome and macrophage activation syndrome.[3] Some of these children tested positive for SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and/or had a positive serological response for this infection. The specific link with SARS-CoV-2 remains unclear.

In Spain, this phenomenon has also been observed.

Objective

In this case series, we intended to describe the epidemiological and clinical features of children with MIS-C in Spain.

Methods

This is a case series of children with MIS-C associated with SARS-CoV-2 enrolled in the Epidemiological Study of COVID-19 in Children of the Spanish Society of Pediatrics (EPICO-AEP), from March 1st to June 1st, 2020. EPICO-AEP is a multicenter national study aiming to describe the COVID-19 in Spanish children. Children younger than 18 years with infection due to SARS-CoV-2 and attended at 49 hospitals were included in this registry. Inclusion criteria included positivity in real-time polymerase chain reaction (RT-PCR) positive, IgM or IgG in lateral-flow rapid test, ELISA or immuno chemiluminescence serology (see Table 1), or severe disease suggestive of MIS-C and recent household contact with a confirmed patient with COVID-19.

Results

By June 1st, 312 patients had been attended in the 49 hospitals, and 252 participants were hospitalized. Of them, 181 (72%) were admitted due to causes directly or likely related to SARS-CoV-2. The remaining 71 (28%) were admitted due to causes not related with SARS-CoV-2, but were screened and found to be infected with SARS-CoV-2. A total of 31/252 (12%) children were diagnosed as MIS-C and/or Kawasaki disease by their physicians.

Weekly admissions of children with MIS-C and children with other clinical presentations associated with COVID-19 were recorded (Figure 1). The peak of MIS-C cases was one month after the peak of admissions for other COVID-19 related reasons and decreased afterward.

Median age and interquartile range were 7.6 [4.5;11.5] years. A total of 30 (97%) children had microbiological or serological evidence of SARS-CoV-2 infection, and the remaining patient, an 11-year old boy with incomplete Kawasaki disease and pericardial effusion, had epidemiological household contact with a COVID-19 adult patient (his father, who is a health worker). Seventeen children (17/31; 55%) had positive SARS-CoV-2 RT-PCR in any of up to 2 respiratory samples (nasopharyngeal/oropharyngeal swab or bronchial aspirate), IgM was positive in 10/17 (59%) and IgG in 19/21 (90%). All patients with IgM positive had also IgG positive. Seven out of 21 (33%) patients had both RT-PCR and IgG positive, and 16/29 (52%) had a household contact with a confirmed COVID-19 patient (see supplementary table S1 for details on microbiological and serological results).

The World Health Organization recently released diagnostic criteria for this condition. [4] All the described patients fulfilled the WHO case definition for MIS-C, except for 1/31 patients (3%).

Rash or bilateral non-purulent conjunctivitis, or muco-cutaneous inflammation signs were found in 21/31 (67%) patients; hypotension or shock in 15/31 (48%), features of myocardial dysfunction 25/31 (80%) consisting of pericarditis, valvulitis, arrhythmias or coronary abnormalities in 19/31 (61%); 6 (19%) additional children had only an elevation of a biochemical marker of heart dysfunction (NT-proBNP); evidence of coagulopathy (specifically, elevated D-dimers) was found in 29/30 (97%), and acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain), in 27/31 (87%). No other apparent microbial cause of inflammation as sepsis or staphylococcal or streptococcal shock syndrome was found.

The patient who does not include WHO criteria was a 12-month old girl. The criterion she did not meet was the elevation of inflammatory markers. She was cohousing with a COVID-19 patient. She was on chronic oral treatment with steroids due to a chronic idiopathic interstitial lung disease. She presented with 6 days of fever, shortness of breath and cardiogenic shock (pH=7.2). She had lymphopenia (1,100 cells/mm^3). She was diagnosed with cardiogenic shock. Echocardiography showed left ventricle dilatation above +2.6 Z-score for age and sex, and ejection fraction of 55%. Enterovirus infection was ruled out with PCR in nasopharyngeal aspirate. She received 10 days of remdesivir. Although she had low inflammatory markers, this fact was attributed to the long-term immunosuppressive therapy with steroids. She had a coinfection with human metapneumovirus (hMPV). She was treated for MISC with intravenous immunoglobulin (IVIG) and steroids. She was on long-term oral steroids due to pulmonary interstitial disease, which may avoid the rising of acute-phase reactants.

Thirteen children (45%) fulfilled the criteria of complete or incomplete Kawasaki disease. Other clinical features and laboratory values are summarized in Table 1.

Twenty (65%) patients needed admission to the Pediatric Intensive Care Unit, and 6/31 (19%) invasive mechanical ventilation. Cardiac complications consisted of myocardial dysfunction (15/31; 48%), pericardial effusion (6/31; 19%); valvular dysfunction (9/31; 29%), arrhythmias (7/31; 23%) and coronary abnormalities (3/31; 10%, among them 1 aneurysm). Four patients (13%) had renal failure.

Two (6%) patients received remdesivir and 7/31 (23%) lopinavir/ritonavir. A total of 21/31 (68%) children received corticosteroids: 19 of these received methylprednisolone (13 patients received doses of 1 to 2.5 mg/kg/day; 2 patients boluses of 8 and 30 mg/kg/day for 3 days; 4 had dosing not available), 20/31 (65%) patients received 2 gr/kg of intravenous immunoglobulin (IVIG) and 13/31 (42%) patients received both IVIG and corticosteroids. All but three patients received broad-spectrum antibiotics.

One patient with acute leukemia and bone marrow transplant died, and one 6-month-old patient developed anterior-descendant coronary aneurysm (z-score +9). This patient was an infant with Down syndrome, who presented with 5 days of fever, shortness of breath and shock due to myocardial dysfunction. He had a a positive RT-PCR for SARS-CoV-2 at diagnosis and coinfection with hMPV, proBNP=9,968 pg/mL and troponin I=34.1 ngr/mL. He developed valve insufficiency, renal failure, coronary aneurysm, and eventually had 50 days of fever despite treatment for infection (antiviral treatment with 2 days with lopinavir/ritonavir, hydroxychoroquine, cefotaxime, vancomycin and meropenem, micafungine) and for Kawasaki disease (IGIV and steroids). The rest of the patients recovered without sequels.

Discussion

In this registry, entry criteria was COVID-19 disease, differently from the previous reports that include patient without SARS-CoV-2 [1,3]. Previous reports raised discussion as some children with MIS-C or Kawasaki disease lacked evidence of infection with SARS-CoV-2. Disease triggered by other causes may have been included within those reports. Our data strongly support the idea that not only there is a temporal association with SARS-CoV-2, but also a microbiological association.

In this report, only 1 patient without microbiological or serological evidence of SARS-CoV-2 was included, but he had a strong epidemiological link. There is a possibility that not all MIS-C cases are microbiologically related to SARS-CoV-2, because RT-PCR and serology do not have 100% sensitivity and specificity. That is why we have included a patient with negative tests and with recent contact with a patient with COVID-19, according to WHO definition of MIS-C.

Some children included may present other viral infection matching criteria of MIS-C and a positive test for SARS-CoV-2 reflecting only past or asymptomatic infection. Also, some children with acute COVID-19 might fulfil WHO criteria. On the other hand, children with Kawasaki disease may fit the WHO case definition and could have positive tests for SARS-CoV-2 simply because the virus is so widely circulating. This may happen with the 6-months infant reported, but given the cardiogenic shock, the proBNP figures and additional features, we considered the disease as MIS-C. With all their limitations, only consensus criteria are currently available. According them, our data points to a microbiological relationship between SARS-CoV-2 and MIS-C.

Limitations of this study include that some cases without microbiological, serological or epidemiological link may not have been included in this registry.

SARS-CoV-2 could be a relevant trigger for a delayed cytokine storm and an inflammatory condition, with potentially severe consequences.[6] Coinfections as hMPV may be present and might play a role in triggering the immune response. It is possible that some particular patients with special features – as chronic immunosuppressive treatment influencing inflammatory markers - may have MISC but not fulfill all WHO criteria.

Conclusions

MIS-C is a potentially severe condition that presents in some children after SARS-CoV-2 infection. Until herd immunity or a vaccine are available, physicians should be aware of this severe condition in children during COVID-19 epidemics. More studies are necessary to clarify the physiopathology of this syndrome and its adequate treatment.

NOTES

Author Contributions:

AT, and CM conceptualized and designed the study. MS performed data management and statistical analysis. CM and AT drafted the manuscript. All co-authors enrolled participants and participated in the collection of data. All co-authors participated and were involved in the critical review of the final manuscript.

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Table 1. Clinical, microbiological and laboratory features of children with multisystemic inflammatory syndrome associated with SARS-CoV-2 in Spain.

Footnote:

*All patients with IgM positive had also IgG positive.

**Test used and performance according manufacturers: Immunochemoluminescence Abbot™ SARS-CoV-2, (S=96% at 14 days, Sp=99.6%), n=15; Euroimmun™ (Sensitivity [S]=94%, Specificity [Sp]=100%), n=4; Immunochemoluminescence Diasorin™ SARS-CoV-2 S1/S2 IgG, S=97%, E=98%, n=1; ELISA in-house total antibody test, included within Solidarity II trial, ongoing and results pending, n=6; Rapid Test BioZek™, IgM (S=85%, Sp=96%), IgG (S=99.9%, Sp=88%), n=3; Immunoassays Elecsys SARS-CoV-2 Cobas™, total antibodies, S=84%, Sp=100%, n=2.

Categorical Features	Observed Cases / Patients
Demographic	
Male	18/31 (58%)
Comorbidities	

Asthma	4/31 (13%)
Obesity	3/31 (10%)
Chronic cardiac disease	1/31 (3%)
Chronic hematologic disease	1/31 (3%)
Neoplasm	1/31 (3%)
SARS-CoV-2 evidence	
Reverse-transcriptase PCR positive	17/31 (55%)
IgM for SARS-CoV-2 positive*, **	10/17 (59%)
IgG for SARS-CoV-2 positive**	19/21 (91%)
Reverse-transcriptase PCR positive and IgG for SARS-CoV-2 positive	7/21 (33%)
Any microbiological test positive	30/31 (97%)
Close contact with a COVID-19 patient	16/31 (52%)
Co-detections	6/21 (29%)
SARS-CoV-2 and metapneumovirus	2/21 (10%)
SARS-CoV-2 and IgM positive for *M. pneumoniae*	1/21 (5%)
Clinical features	
Fever ≥3 days	30/31 (97%)

Rash or bilateral conjunctivitis	23/31 (74%)
Hypotension or shock	15/31 (48%)
Gastrointestinal problems (abdominal pain, vomits, diarrhea)	27/31 (87%)
Fatigue / Malaise	15/29 (51%)
Cough	11/31 (36%)
Shortness of breath	8/30 (27%)
Sore throat	8/31 (26%)
Myalgia	5/28 (18%)
Headache	6/29 (21%)
Altered consciousness / confusion	4/31 (13%)
Lymphadenopathy	4/31 (13%)
Outcome	
Died	1/31 (3%)
Cardiological complications	19/31 (61%)
Myocardial dysfunction	15/31 (48%)
Pericardial effusion	6/31 (19%)
Valvular dysfunction	9/31 (29%)

Arrhythmias		7/31 (23%)
Coronary abnormalities		3/31 (10%)
Continuous Features	**Observations**	**Median [IQR]**
Age (years)	31/31 (100%)	7.6 [4.5;11.5]
Total days of fever	30/31 (97%)	6.00 [5.00;8.00]
Days of fever at admission	30/31 (97%)	5 [3.00; 6.00]
Heart rate at admission for (beats per minute)	30/31 (97%)	127 [118;148]
Respiratory rate at admission (breaths per minute)	18/31 (58%)	30.0 [27.0;34.8]
Oxygen saturation at admission (room air)	29/31 (93%)	98.0 [96.0;99.0]
C-reactive protein (mg/L), worst value	31/31 (100%)	166 [83.7;233]
Procalcitonin (ng/mL), worst value	29/31 (94%)	6.74 [1.65;10.8]
D-Dimer (ng / mL), worst value	30/31 (97%)	2896 [2059;5355]
IL-6 (pg / mL), worst value	23/31 (74%)	133 [41.3;324]
Ferritin (ng/mL), worst value	29/31 (94%)	627 [365;1278]
NT-proBNP (pg/mL), worst value	22/31 (71%)	8918 [4136;14255]
Hemoglobin (g/dL), worst value	31/31 (100%)	10.3 [9.00;11.2]
Leukocytes (cells/mm3), worst value	31/31 (100%)	9560 [7365;17850]

Neutrophils (cells/mm3), worst value	30/31 (97%)	6810 [5725;14355]
Lymphocytes (cells/mm3), worst value	31/31 (100%)	910 [500;1700]

FIGURE LEGEND

Figure 1. Weekly number of admissions of children due to multisystem inflammatory syndrome associated with SARS-CoV-2 (green) and due to other presentations of COVID-19 (orange).

Figure 1