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Multisystem Inflammatory Syndrome in Children associated with COVID-19: Report of four cases in Mexico across the Mexico-US Border

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ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly described autoimmune disease mostly occurring in older children, adolescents, and young adults associated with Severe Acute Respiratory Syndrome-Coronavirus type 2 (SARS-CoV-2) infection. Several MIS-C publications from Europe and North America are available, with only a few from Latin America. This is the first Mexican publication of four case reports of MIS-C. Median age at admission was of 8.2 years. All cases manifested with fever, cutaneous rash, conjunctivitis, abdominal pain, and nausea/vomiting. All were admitted with shock, developed coronary abnormalities in the echocardiogram, and had lung abnormalities in the computerized tomography scan. Three needed medical care at the Pediatric Intensive Care Unit, all were resistant to intravenous immunoglobulin, and one patient died of severe myocarditis, shock and acute myocardial infarction. All four cases had a positive SARS-CoV-2 RT-PCR from nasopharynx.

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Introduction

On April 24th/2020, the Rheumatology Study Group of the Italian Pediatric Society issued an alert to the medical society regarding the increase in cases of incomplete or atypical Kawasaki Disease (KD) with greater resistance to intravenous immunoglobulin (IVIG), trend towards macrophage activation syndrome (MAS), and admission to the Pediatric Intensive Care Unit (PICU). In several of these children, evidence of recent SARS-CoV-2 infection was documented by laboratory, or there was a history of contact with positive relatives for the virus [1].

Soon after the Italian publication, several other studies have been published in Europe, particularly in France and the UK [2-6].

In the US, New York was the first state where MIS-C was detected and followed by National American data just recently published [7,8].

It was initially named as Pediatric Inflammatory Multisystem Syndrome (PIMS), but currently known as Multisystem Inflammatory Syndrome in Children (MIS-C), with well described diagnosis criteria by both the WHO and the American College of Rheumatology [9, 10].

There are a few Latin American MIS-C reports and case series [11-14], being our study the first peer-reviewed Mexican publication of four cases in two hospitals, right across the US-Mexican border, the most transited in the globe [15].

Materials and Methods

Since May 1st until July 30th/2020, prospective surveillance actively looking for patients with MIS-C based on the WHO definition criteria was established at the General Hospital of Tijuana, Baja-California, Mexico, and the Hospital #31 of the Mexican Institute of Social Security, Mexicali, Baja-California, Mexico [9]. These two hospitals, since the beginning of the pandemic in Mexico in March/2020, are only admitting patients with COVID-19, and so called "COVID-19 Hospitals".

All patients were clinically and laboratory (Cell Blood Count (CBC), Liver Functional Tests, Blood Chemistry, Erythrocyte Sedimentation Rate (ESR), blood cultures, among others) evaluated at admission, and when needed. Both a thoracic computerized scan (CTS) and echocardiogram was done to each patient during hospitalization, and confirmation of SARS-CoV-2 infection was done by RT-PCR from nasopharynx (MCD Servicios Integrales® S.A de C.V, Mexico) which detects both E (Envelope) and N (Nuclear) SARS-CoV-2 genes.

All patients received the recommended standard of care for every complication as internationally suggested at the time they were hospitalized, and as needed based on their clinical/paraclinical outcome.

This was only an observational study, and approved by the local IRB. Only descriptive non—comparative statistical tests were used.

Results

During these three months (May-July/2020) of active surveillance, four cases of MIS-C were diagnosed, and admitted on June (one patient) and July (three). Median age was of 8.2 years (9 months – 14 years old), half were male and half female. All cases manifested with fever (median of 5 days prior to admission), cutaneous rash, non-suppurative conjunctivitis, limbs' edema and erythema, oral mucositis and lips cheilitis, abdominal pain, and nausea/vomiting. Each child was admitted with signs and symptoms of shock. Laboratory findings at admission revealed mild anemia, leukocytosis with neutrophilia, and elevated ESR in all patients, with mild thrombocytopenia and elevated aminotransferases in two. All patients revealed coronary dilations in the echocardiogram, with one also presenting myocarditis. All four children had abnormal CTS (from ground glass images in three, to consolidated infiltrates in one). Three were admitted at the PICU. Regarding treatment, all were resistant to IVIG (received two doses due to persistence of fever following 36 hours after the final infusion of the first dose), enoxaparin was administered to three children, and two received dexamethasone, inotropic drugs, aspirin, hydroxychloroquine, and tocilizumab. Median hospitalization days was of 10 (5-22). All four cases had a positive SARS-CoV-2 RT-PCR from nasopharynx, nevertheless, there was no positive history of COVID-19 disease in any relative of all four patients. One child, the only who required mechanical ventilation, died of severe myocarditis, shock and acute myocardial infarction.

A summary of the most relevant individual clinical and laboratory findings at admission, as well as treatment and outcomes can be seen in Tables 1 and 2, respectively.

Table 1: Clinical and Laboratory Findings at Admission

Patient	Gender	Age in months	Positive Covid-19 RT-PCR?	First Dx at Admission	Days with Fever at Admission	Signs of Shock at Admission	Non Suppurative Conjunctivitis	Mucositis and Cheilitis	Cervical Lymphadenopathy >1.5cm	Limbs Edema, and Erythema	Cutaneous Rash	Abdominal Pain	Vomiting/ Diarrhea	Respiratory Distress	Blood Leukocytes (%PMN´s)	Platelets	ESR (mm/h)	Elevated Amino transferases
#1	F	120	Yes	Septic Shock	7	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	41,790 (84%)	146,000	46	No
#2	M	154	Yes	Ricketssiosis	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	20,860 (69%)	139,000	14	Yes
#3	M	9	Yes	MIS-C	3	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	42,730 (67%)	193,000	17	Yes
#4	F	42	Yes	Kawasaki Disease and Acute Abdomen	5	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	11,600 (88%)	290,000	31	No

Dx: Diagnosis; PMN´s: Polymorphonuclear Leukocytes; ESR: Erythrocyte Sedimentation Rate;

Table 2: Treatment and Outcome

Patient	Gender	Age in Months	Thoracic CT-Scan	Abnormal Echocardiogram	Second Dose of IVIG Administered?	Use of Steroids?	Use of Tocilizumab?	Use of Aspirin?	Use of Enoxaparin?	Use of Hydroxychloroquine?	PICU Hospitalization?	Mechanical Ventilation?	Use of Inotropics?	Death?	Hospitalization days
#1	F	120	Abnormal	Coronary Dilatation, and Myocarditis	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes. Shock ,and Acute Myocardial infarction	11
#2	M	154	Abnormal	Coronary Dilatation	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	9
#3	M	9	Abnormal	Coronary Dilatation	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	22
#4	F	42	Abnormal	Coronary Dilatation	Yes	No	No	Yes	No	No	Yes	No	No	No	5

CT: Computerized Tomography; IVIG: Intravenous immunoglobulin;

In addition, as seen in Figure-1, the COVID-19 pandemic in the state of Baja-California, Mexico, started in early March/2020, and reaching a high plateau of total confirmed cases on May, June, and July. Our four MIS-C cases appeared in June and July during these three months of active surveillance.

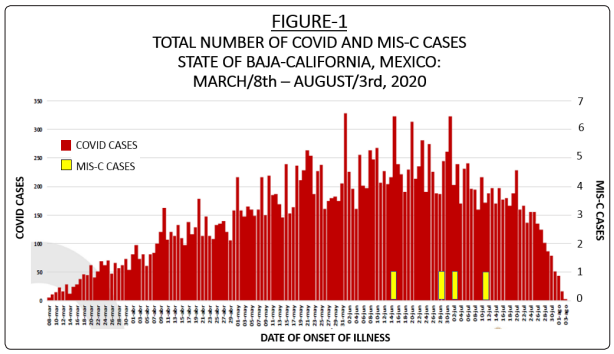

FIGURE-1
TOTAL NUMBER OF COVID AND MIS-C CASES
STATE OF BAJA-CALIFORNIA, MEXICO:
MARCH/8th – AUGUST/3rd, 2020

Discussion

Studies done in France, Italy, the UK and the US have clearly shown that MIS-C is a new autoimmune SARS-CoV-2 triggered disease, affecting mostly older children, adolescents, and young adults, it resembles incomplete or atypical KD, however, the latter affects mostly children < 5 years of age, whereas MIS-C in older ages, and is associated with greater resistance to IVIG, trend towards macrophage activation syndrome (MAS), and admission to the PICU due to a much higher severity of the disease [1-8]. In several of these children, evidence of recent SARS-CoV-2 infection could be documented by laboratory, or there was a history of contact with positive relatives for the virus [1-12]. In our study, all four cases were confirmed by SARS-CoV-2 RT-PCR, however, surprisingly, no clinical history of COVID-19 cases within their families.

Both publications from developed and Latin American countries (particularly the largest one performed in Chile with 27 cases) described MIS-C as a disease with the potential of several cardiological, pulmonary, hematologic, abdominal, and neurologic complications, among others, and, as mentioned, usually resistant to one dose of IVIG, and requiring multiple other interventions such as anti-inflammatory monoclonal antibodies, inotropic drugs, anticoagulant therapy, and even mechanical ventilation, among others[1,8,11,13,14]. Our study did not differ from all those studies, in which all four patients were admitted with shock and resistant to IVIG, three needed to be admitted at the PICU, three received enoxaparin, two inotropic drugs, and one died.

Additionally, even though the number of cases is low, our four patients with MIS-C occurred after two months when the COVID-19 pandemic started in our state, resembling the epidemiological features of MIS-C both in Europe and the US, in which most of cases also started months after the pandemic started. The reason(s) for these phenomena are still unclear [1-14].

Conclusions

As elsewhere in the world, MIS-C is a disease that should carefully and intensively be monitored as a result of the COVID-19 pandemic, due mostly to its severity, but also to the increasing number of cases reported worldwide.

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