Case Report

Multisystemic Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection: A Case Series Report in a Pediatric Center in Mexico

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Abstract

We report four cases of patients with multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, of which three patients presented characteristics of Kawasaki disease (KD). All presented fever of more than 3 days, and gastrointestinal involvement, significant increase in C-reactive protein (CRP), polymorphonuclear cells, procalcitonin, D-dimer, fibrinogen and troponin, lymphopenia and hypoalbuminemia. Myocardial involvement was observed in two patients. All were treated with fluids resuscitation and vasoactive therapy, 75% received intravenous immunoglobulin (IVIG) and systemic steroids. Two patients developed a transient acute kidney injury, one patient presented as acute appendicitis and developed a bilateral pleural effusion. One patient required a second dose of IVIG and boluses of methylprednisolone. None required mechanical ventilation and there were no deaths.

Keywords: SARS-CoV-2; COVID-19; Multisystem inflammatory syndrome in children; Kawasaki disease; Kawasaki disease shock syndrome; Myocarditis

Introduction

The emergence of a new respiratory virus, from the beta-corona-
required an emergency operation for suspected appendicitis, which was finally diagnosed as mesenteric adenitis. The echocardiogram showed myocardial involvement in two cases, but did not find coronary abnormalities.

A significant increase in C-reactive protein (CRP), polymorphonuclear cells, procalcitonin, D-dimer and fibrinogen was observed, as well as lymphopenia and hypoalbuminemia.

All patients received fluid resuscitation and vasoactive therapy (epinephrine or norepinephrine) for at least 24 - 48 h due to hypotension; all received broad-spectrum antibiotics, without isolation of germ in blood cultures. Three patients received intravenous immunoglobulin (IVIG) (2 g/kg/dose) and three boluses of methylprednisolone (10 - 30 mg/kg/dose).

Two patients developed acute kidney injury with recovery of kidney function 72 h after IVIG and methylprednisolone treatment. The patient who presented with acute appendicitis had an insidious evolution with ascites, bilateral pleural effusion, mild pericardial effusion, pulmonary arterial hypertension and severe tricuspid regurgitation, with persistence of fever at 36 h, elevated leukocytosis, CRP and D-dimer. A second dose of IVIG was administered, as well as methylprednisolone boluses, enoxaparin, and bilateral intercostal drainage, with recovery 3 weeks after admission. None required mechanical ventilation and there were no deaths. Everyone is at home without medication and without complications.

Discussion

SARS-CoV-2 infection in pediatric age has been reported around 1-4.3%, generally asymptomatic course to mild forms. At the end of April 2020 the first cases of a new entity called MIS-C with clinical findings similar to KD, KD shock syndrome (KDSS) and toxic shock syndrome was reported [4]. On May 1, 2020, the Royal College of Paediatrics and Child Health (RCPCH) published a case definition and guidance related to this multisystem illness, defining it as a child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features. This may include children fulfilling full or partial criteria for KD; exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus, and SARS-CoV-2 PCR test results may be positive or negative [4-8].

Cases have increased from tens to hundreds in several countries, with different series similarities with a greater number of cases (Table 1 [9-13]): median age between 7.5 and 11 years, male predominance from 51% to 66%, confirmation of SARS-CoV-2 by nasopharyngeal RT-PCR and/or IgG/IgM serology in 65-90%, gastrointestinal involvement (vomiting, diarrhea, or abdominal pain) in more than 80%, shock in 50-90%, and myocardial dysfunction in one to two thirds of patients. Complete, incomplete KD or KDSS occurred in half of the cases due to the presence of bilateral conjunctivitis, oral changes, skin rash, and edema of the hands and feet. Laboratory findings are consistent with lymphopenia and hypoalbuminemia, marked elevation of CRP, procalcitonin, ferritin, fibrinogen, D-dimer, troponin I, and N-terminal pro-brain-type natriuretic peptide (NT-proBNP). Coronary artery abnormalities occur in one third of cases, while the development of coronary aneurysms ranges from 8% to 23%. The initial treatment was IVIG (2 g/kg) in 70-100%, a second dose of IVIG up to 20%, systemic steroids (2-10 mg/kg/day) in 34-73% and biological therapy (anti interleukin-1 (IL-1) or IL-6) in 8-20%; and liquid resuscitation, vasoactive and inotropic agents in 40-80%. Mortality is less than 2.5% [9-13].

The effort to understand the immunopathology of the SARS-CoV-2 infection since the beginning of the pandemic and to establish the appropriate treatment, aimed at avoiding the serious forms and complications described under a constellation of symptoms and biochemical findings of a so-called “torn of cytokines”, which is characterized by hyperinflammation that generates multiorgan and myocardial dysfunction, due to the excessive release of cytokines (IL-1β, IL-6, IL-8 and interferon gamma (INFγ)) secondary to uncontrolled immune activation, commonly observed in autoimmune diseases such as juvenile idiopathic arthritis systemic, Still’s disease, systemic lupus erythematosus, as well as macrophage activation syndrome, evidenced by cytopenias, coagulopathy, hepatitis, disseminated intravascular coagulation, and hyperferritinemia [14].

MIS-C is considered to be caused by a late response to SARS-CoV-2 infection, as some patients have a negative RT-PCR but a positive IgM/IgG serology, highlighting the involvement of aberrant innate immunity as the main mechanism. There is also evidence that antibodies to SARS-CoV-2 accentuate the disease through a facilitating mechanism that enhances viral entry or antibody replication as has been observed in dengue [15].

Three disease patterns are recognized in children hospitalized for MIS-C. The first group, with persistent fever and high levels of inflammation markers, but without characteristics of KD, shock or organ dysfunction; the second group, with criteria for KD; and the third group, with shock and clinical, echocardiographic and laboratory evidence of myocardial injury [12]. Three of the cases we present have characteristics of KD with abdominal pain and shock. All responded adequately to forced resuscitation with fluids, IVIG, steroids, and vasopressors.

Conclusions

Various pediatric centers are recognizing the various MIS-C phenotypes around the world, with identification of risk factors, pathogenesis, clinical course, and treatment for MIS-C. These are the first cases we identified in our pediatric care center, which posed a challenge in diagnosis and treatment. Better understanding of MIS-C will allow us to recognize this serious and potentially fatal entity.

Supplementary Material

Suppl 1. Clinical characteristics, laboratory, echocardiogram, treatment and outcomes of the four patients with COVID-
Table 1. Overview of the Various Series With Multisystemic Inflammatory Syndrome in Children

| Author            | County | Whittaker et al, 2020 [10] | Feldstein et al, 2020 [11] | Davies et al, 2020 [12] | Belhadjer et al, 2020 [13] |
|-------------------|--------|--------------------------|---------------------------|------------------------|--------------------------|
| Patients          | France | 21                       | 58                        | 186                    | 78                       |
| Median age (year) |        | 7.9                      | 9                         | 8.3                    | 11                       |
| Male (%)          |        | 43                       | 66                        | 62                     | 66                       |
| KD complet/incomplete (%) |        | 55/NA                    | 22/NA                     | 20.4/19.3              | NA                       |
| KDSS (%)          |        | 57%                      | -                         | -                      | NA                       |
| Epidemiological contact (%) |        | 48                       | 29.5                      | NA                     | 37                       |
| SARS-CoV-2 positive (%) |        | 90                       | 78                        | 70                     | 64                       |
| Gastrointestinal system (%) |        | 100                      | 45.53                     | 92                     | 90                       |
| Shock (%)         |        | 57                       | 50                        | NA                     | 87                       |
| Myocardial dysfunction (%) |        | 76                       | 31                        | 33                     | NA                       |
| Neurological system (%) |        | 29                       | 26                        | 7                      | 87                       |
| Laboratory findings |        | ▼ Lymphocytes, albumin and serum sodium; ▼ CRP, procalcitonin, ALT, DD, NT-proBNP and IL-6 | ▼ Lymphocytes, albumin serum; ▼ CRP, ferritin, neutrophils, troponin I and NT-proBNP | ▼ Lymphocytes, albumin serum and platelets; ▼ CRP, ferritin, neutrophils, troponin I and NT-proBNP, and ALT | ▼ Lymphocytes, platelets; ▼ CRP, ferritin, DD, fibrinogen, troponin I and NT-proBNP, and ALT | ▼ Lymphocytes, ▼ CRP, troponin I, ferritin, DD and IL-6 |
| CAA (%)           |        | 24                       | NA                        | NA                     | 36                       |
| Coronary aneurisms (%) |        | 0                        | 14.5                      | 8                      | 23                       |
| IVIG (%)          |        | 100                      | 71                        | 77                     | 76                       |
| Second dose IVIG (%) |        | 24                       | NA                        | 21                     | NA                       |
| Systemic steroids (%) |        | 48                       | 64                        | 49                     | 73                       |
| Fluid resuscitation (%) |        | 52                       | 79                        | NA                     | 92                       |
| Vasoactive and inotropic agents (%) |        | 71                       | 47                        | 48                     | 83                       |
| Mechanical ventilation (%) |        | 52                       | 43                        | 20                     | 46                       |
| Biologic therapy (%) |        | 0                        | 19                        | 21                     | 22                       |
| Anticoagulation therapy (%) |        | 0                        | 0                         | 47                     | 50                       |
| Death (%)         |        | 0                        | 2                         | 2                      | 2.5                      |

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IVIG: intravenous immunoglobulin; KD: Kawasaki disease; KDSS: KD shock syndrome; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase, LDH: lactate dehydrogenase; DD: D-dimer; NT-proBNP: N-terminal pro-brain-type natriuretic peptide; CAA: coronary artery abnormalities; NA: not available; IL: interleukin.
19-related multisystem inflammatory syndrome in children.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained.

Author Contributions

MG, YM, AL, and CV were the treating physicians and did the monitoring of the disease. MG wrote the manuscript with the support from ET; and GP supervised the project. All authors discussed the results and contributed to the writing of the final manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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