

Cardiology compromise and inflammatory markers in children with Multisystemic Inflammatory Syndrome related to COVID-19 infection

Compromiso cardiológico y marcadores inflamatorios en niños con Síndrome Inflamatorio Multisistémico relacionado a la infección por COVID-19

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What do we know about the subject matter of this study?

MIS-C is a pathology of the pediatric patient, which manifests weeks after coronavirus infection, clinically similar to Kawasaki disease, toxic shock, and macrophage activation syndrome. It is caused by an exaggerated post-infectious immune response. Cardiological involvement is frequent, its etiopathogenesis is unknown, and cardiological manifestations are generally mild.

What does this study contribute to what is already known?

The objective of this research is to describe and compare the cardiological involvement and inflammatory markers in patients with MIS-C, in order to contribute to the knowledge and management of this new entity in the local population.

Abstract

Coronavirus 2 (SARS-CoV-2) infection has spread rapidly. In pediatrics, a condition similar to shock is described named multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). The mechanisms of cardiological involvement are not clear. **Objective:** To describe cardiological involvement and inflammatory markers in hospitalized patients with MIS-C in a tertiary hospital. **Patients and Method:** Observational, retrospective study in children under 15 years of age with MIS-C. Demographic, clinical, and laboratory variables were collected from an electronic platform, including troponin, B-type natriuretic peptide (proBNP), ultrasound, and electrocardiogram. Patients with / without cardiological involvement (CCC / SCC) were compared. GraphPad QuickCalcs® 2018 Software was used for statistical analysis, considering $p < 0.05$. **Results:** Thirteen patients diagnosed with MIS-C, 9 males, median age 9.5 years. All presented with fever and

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abdominal pain, adding one or more of the following symptoms: vomiting, exanthema, diarrhea, altered mucous membranes and/or edema. Five patients had hemodynamic compromise, 9/13 were categorized as CCC. Troponins were elevated 4.1 times in CCC ($p < 0.05$), median ProBNP CCC 6940 pg/ml vs 921 pg/ml in SCC ($p < 0.05$), median Ferritin CCC 482 vs 154 ng/ml in SCC ($p < 0.01$), platelets CCC 106,000 vs SCC 207,000/mm³ ($p < 0.05$). Echocardiogram showed pericardial effusion ($N = 6$), mild systolic dysfunction ($N = 4$), moderate dysfunction ($N = 1$) and coronary alterations ($N = 3$). In the ECG, 3 patients presented transient repolarization disturbance and 1 first-degree atrioventricular block. None required support with extracorporeal membrane oxygenation, with no deaths. **Conclusion:** cardiological involvement in hospitalized children with MIS-C is frequent. Our series showed nonspecific and transitory symptoms, and hemodynamic compromise which responded early to medical treatment, with a favorable evolution. The markers in CCC patients were troponin, ProBNP, ferritin, and thrombocytopenia. The most frequent ultrasound finding was pericardial effusion. The importance of both clinical and laboratory cardiologic evaluation in these patients is evident.

Introduction

Severe acute respiratory syndrome secondary to coronavirus 2 (SARS-CoV-2) infection has rapidly spread worldwide since the first cases identified in China in late 2019¹, being declared a pandemic by the World Health Organization (WHO) on March 11, 2020². Since the first descriptions, reports have identified a low incidence of acute infection in children, in whom the predominant manifestation is mild respiratory symptoms, with a minority requiring hospitalization and intensive care³. In April 2020, reports from the United Kingdom and Italy show a new presentation in children similar to Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome^{1,4}. Since then, a series of affected children with the same features have been reported in other regions of the world. This condition was defined as “multisystem inflammatory syndrome in children” (MIS-C) by the Center for Disease Control and Prevention (CDC) on May 14, 2020, and as “pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2” (PIMS-TS) by the WHO^{4,5}. It is proposed to be secondary to a post-infectious immune response since most patients present antibodies against SARS-CoV-2 in the etiological study⁶.

These studies describe that MIS-C occurs weeks after the peak of COVID-19 cases, which has occurred in our country, reporting 174 cases in March 2021 (Ministry of Health report March 2021) in 27 pediatric health centers from the Antofagasta to the Puerto Montt Region.

To date, case reports have shown a high incidence of cardiovascular involvement, with cardiac alterations being described in up to 80%. Reported alterations include coronary involvement, myocardial injury, myocarditis, ventricular dysfunction, pericarditis, valvulitis, arrhythmias, elevated cardiac biomarkers [tro-

ponin and B-type natriuretic peptide (proBNP)], and shock^{7,8}.

Currently, the mechanisms of myocardial involvement in MIS-C are not well identified. Possible causes include severe systemic inflammation, acute viral myocarditis, hypoxia, and, infrequently, ischemia due to coronary involvement⁶, and it is proposed that ventricular dysfunction may result from a combination of these mechanisms⁴.

A rapid improvement in ventricular function has been described after immunomodulatory treatment, reporting around 50% of involvement in the initial evaluation, with a significant improvement observed after 30 days of follow-up⁹. Coronary alterations have been reported in about 20% of cases, which have also presented a favorable response to immunomodulatory management¹⁰. Kelly et al. report pericardial effusion in 30%, mild to moderate mitral insufficiency in 25%, and tricuspid regurgitation in 17% of cases¹¹. Significant arrhythmias in pediatric patients with MIS-C are infrequent but present a higher incidence than in the general population, reported in about 12%¹².

Rapidly recovering shock has been observed in 32-76% in the series described⁴. Given the severity of cardiovascular involvement in this syndrome, it is necessary to characterize the cardiac alterations in these patients in order to define prognostic factors and responses to currently applied therapies. The objective of this study was to describe and compare the cardiologic involvement and inflammatory markers in children admitted due to MIS-C at the *Hospital Luis Calvo Mackenna* (HLCM) between May and August 2020.

Patients and Method

Observational and retrospective study including 13 children under 15 years of age, diagnosed with MIS-C

according to the 2020 CDC criteria, admitted from May 1 to August 31, 2020, to the HLCM. This study is part of the original study “Clinical, epidemiological, and microbiological characteristics of pediatric cases of covid-19 hospitalized in pediatric hospitals in Santiago, Chile, during the 2020 epidemic outbreak”. It was approved by the Institutional Review Board and by the Ethics Committee for Clinical Research in Humans, Faculty of Medicine, University of Chile. Informed consent was requested from parents and informed assent from children aged 14 years or older. The data were obtained from an electronic platform hosted by the Faculty of Medicine, University of Chile.

The variables obtained were collected from the clinical history, ensuring anonymity and confidentiality. They included: a) demographics: age, sex; b) comorbidities: overweight or obesity and chronic respiratory disease; c) symptoms/signs on admission: fever, dyspnea, abdominal pain, vomiting, diarrhea, exanthema, mucosal alteration, conjunctivitis, limb edema, adenopathy, hypotension, tachycardia; d) laboratory tests: troponin (performed in 2 centers, *Hospital del Tórax* troponin I and HLCM ultra-sensitive troponin I), proBNP, blood count, C-reactive protein (CRP), procalcitonin, D-dimer, ferritin, fibrinogen, albumin, lactate dehydrogenase (LDH), lactate; e) cardiac alterations: echocardiogram and electrocardiogram (ECG); f) treatment: use of acetylsalicylic acid (ASA), corticosteroids, intravenous gamma globulin (IVIG), anticoagulant therapy, use of mechanical ventilation (MV), vasoactive drugs (VAD), extracorporeal membrane circulation (ECMO), admission to the PICU, days of hospitalization, and mortality. In addition, confirmation of viral infection is performed through nasopharyngeal sample: RT-PCR for SARS CoV-2, (Hamilton extraction automation and Thermo Fisher PCR probe) and rapid serological tests were performed to detect IgM/IgG antibodies against SARS-CoV-2 (AFIAS CoV IgG/IgM kit).

The 2020 CDC definition was used to determine MIS-C, which includes the following criteria: age < 21 years, fever (temperature > 38.0°C for ≥ 24 hours or subjective fever lasting ≥ 24 hours), laboratory evidence of inflammation including, but not limited to, one or more of the following: elevated CRP, erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, LDH, interleukin 6 (IL-6), neutrophils; lymphopenia, hypoalbuminemia associated with clinically severe illness requiring hospitalization, with 2 or more organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurologic), and no alternative plausible diagnoses with a positive test for current or recent SARS-CoV-2 infection (RT-PCR, serology, antigen test) or exposure to COVID-19 within 4 weeks before symptom onset.

Nutritional diagnosis was defined according to WHO criteria as obesity in children aged < 6 years according to weight/height ratio (W/H) ≥ +2 standard deviations (SD), and in those > 6 years according to body mass index for age (BMI) ≥ +2 SD. (Ministry of Health 2018).

Cardiological involvement was considered as the presence of an abnormal ECG and/or altered echocardiogram. The latter was defined as decreased left ventricle function (biplane ejection fraction less than 55%, classified as mild dysfunction between 54-45%, moderate 45-35%, severe < 35%), left ventricular dilatation according to parameters for the patient's body surface area (left ventricular measurement Z score in M mode > 2 with reference Detroit data), pericardial effusion, mitral insufficiency, coronary artery alterations (hyperchogenicity, dilatation, and aneurysms, the last two defined by diameter measurement with Z score > 2 according to Montreal database). All these findings were correlated with the inflammatory markers proBNP and serum troponin I or uSI levels, which were recorded in number of times over the normal limit for each laboratory range (the initial measurement of troponin I was not available at the base center, leading to its purchase as an external service, which explains the existence of two methods of evaluation).

Statistical analysis

Demographic and clinical characteristics were described using frequencies or percentages for categorical variables and measures of central tendency and dispersion for continuous variables. Clinical characteristics and laboratory findings were compared according to cardiac involvement. Inflammatory biomarkers were analyzed according to the most altered test before the initiation of treatment and, regarding cardiac biomarkers, the most altered result during the entire hospitalization was considered.

Comparisons of groups with cardiac involvement (WCI) and with no cardiac involvement (WNCI) were performed using nonparametric tests; Fisher's exact test or Mann-Whitney test according to whether the data were categorical and continuous, respectively. Statistical analyses were performed using QuickCalcs - © 2018 GraphPad Software, considering a two-tailed p-value < 0.05 as statistically significant.

Results

13 patients who met the diagnosis criteria of MIS-C were analyzed. The median age was 114 months (9.5 years), and most were male (N = 9, 69%). The most frequent comorbidities were overweight or obesity (N = 7, 53%) and chronic respiratory pathologies

(N = 5, 38%). Among the most frequent symptoms, abdominal pain was observed in 11 patients (84%), tachycardia in 10 (76%), and vomiting in 9 (69%) (Table 1).

Of the total sample, 9 presented some type of cardiologic involvement, accounting for 69% of the total number of children analyzed. The median age of the WCI patients was 87 months (7.5 years), 89% were male, and the most frequent comorbidity was obesity and overweight (N = 6, 46%). In relation to symptoms and signs in this group, gastrointestinal manifestations were more frequent (abdominal pain 100%, vomiting 66%, diarrhea 66%), in addition to exanthema in 66%, tachycardia 77%, and hypotension in 55% of patients. Lactic acid values were low in all patients, with and without cardiologic involvement.

In cardiological markers, an increase in troponin was observed at 4.1 times the high normal level in WCI vs WNCI patients ($p < 0.05$). Median ProBNP in WCI patients was 6940 pg/ml vs 921 pg/ml in WNCI patients

($p < 0.05$). In WCI, median ferritin was 482 ng/ml vs 154 ng/ml in WNCI ($p < 0.01$), and platelet count was 106,000 vs 207,000 in WNCI ($p < 0.05$) (Table 2).

The most frequent echocardiographic findings were pericardial effusion (N = 6, 67%), mild systolic dysfunction (N = 4, 44%), and mitral insufficiency (N = 4, 44%). Two patients had coronary arteries dilatation (22%) and one presented hyperechogenicity (11%); there were no patients with coronary aneurysms (Table 3).

Of the total number of WCI patients, 8 underwent ECG. Of these, 50% showed abnormalities, 1 with first-degree atrioventricular block and 3 with repolarization abnormalities (Table 3).

The WCI patients received IVIG in 100% of cases, corticosteroids in 88%, low molecular weight heparin (LMWH) in 88%, ASA in 22%, VAD in 33%, and invasive MV in 22%. The median hospital stay was 10 days. There was no need to connect patients to ECMO or deaths in our series (Table 4).

Table 1. Demographic and clinical characteristics of patients diagnosed with MIS-C with and without cardiological involvement

Demographic and clinical characteristics n (%)	Total, of Patients (n = 13)	WITH cardiological compromise (n = 9)	WITHOUT cardiological compromise (4)	p value
Age: middle (p25-p75)	114 (80-124)	87	137.5	
Gender: n				
- Female	4 (31)	1 (14)	3 (75)	0.05
- Male	9 (69)	8 (89)	1 (25)	0.05
Comorbidity: n (%)				
- Overweight or obese	7 (53)	6 (46)	1 (25)	0.26
- Respiratory	5 (38)	3 (33)	2 (50)	1.0
- None	4 (30)	2 (22)	2 (50)	0.53
Symptoms: n (%)				
- Fever	13 (100)	9 (100)	4 (100)	1.0
- Abdominal pain	11 (84)	9 (100)	2 (50)	0.07
- Tachycardia	10 (76)	7 (77)	3 (75)	1.0
- Vomiting	9 (69)	6 (66)	3 (75)	1.0
- Diarrhea	7 (53)	6 (66)	1 (25)	0.26
- Exanthema	7 (53)	6 (66)	1 (25)	0.26
- Dyspnoea	6 (46)	4 (44)	2 (50)	1.0
- Lesiones of mucous	6 (46)	4 (44)	2 (50)	1.0
- Conjunctivitis	5 (38)	4 (44)	1 (25)	1.0
- Hypotension	5 (38)	5 (55)	0	0.1
- Edema	3 (23)	3 (33)	0	0.49
- Lymphadenopathy	2 (15)	2 (22)	0	1.0
COVID Test: n (%)				
- Serology IgG (+)	8 (61)	5 (71)	3 (75)	1.0
- Close contact COVID-19 (+)	7 (53)	3 (42)	4 (100)	0.06
- SARS- CoV2 RCP (+)	5 (38)	3 (42)	2 (50)	1.0

n: number of patients, IgG: immunoglobulin G.

Table 2. Laboratory results in patients diagnosed with MIS-C with and without cardiological involvement

Laboratory results: median (IQR 25-75)	Total Patients (n = 13)	With cardiological compromise	Without cardiological compromise	p value
<i>Cardiology Biomarkers</i>				
Troponin (n times above normal limit)	2.1 (0.285-5.375)	4.1	0.285	0.03
ProBNP (pg/ml)	3310 (991.5-11785)	6940	921	0.01
<i>Inflammatory markers</i>				
D-dimer (ug/ml)	3940 (2635-5477)	3940	2940	0.27
CRP (mg/L)	180 (144-315)	236	162	0.52
PCT (ng/ml)	4.1 (2.6-14.2)	5.35	1945	0.16
Ferritin (ng/ml)	326 (213-639)	482	154	0.01
Fibrinogen (mg- dl)	533.5 (431-695)	602.5	533.5	0.65
Leukocytes (cel/uL)	9730 (6730-10860)	8720	9920	0.93
ALC (milde/ uL)	639 (455-1018)	568	714	0.60
Platelets (miles / mm ³)	126000 (88000-202000)	106000	207000	0.05
Albumin (g/L)	2.8 (2.6-3.35)	2.8	3.9	0.24
LDH (U/L)	243 (209-295)	243	227.5	0.85
Lactic acid	14.9 (11.35-16.27)	14.9	14.7	1.00

IQR: Interquartile Range, n: number of patients, ProBNP: B-type natriuretic peptide, CRP: C-reactive protein, PCT: Procalcitonin, ALC: absolute lymphocyte count, LDH lactate dehydrogenase, LV: left ventricle, ECG: electrocardiogram.

Discussion

The SARS-CoV-2 virus presents us with an unprecedented situation. It is a new pathogen, at a time of communicational and technological globalization that has facilitated its expansion, which has become a pandemic even before its full pathogenic potential is known and before effective management options have been developed to deal with its various clinical manifestations.

In pediatrics, the predominant manifestation is mild respiratory symptoms³. However, the pathology of greatest concern is MIS-C^{1,4}, a condition that requires hospitalization and often management and monitoring in more complex units. Among the cardiological manifestations, pericardial effusion is reported as one of the most frequent (47-100%), in addition to shock, myocarditis, myocardial dysfunction, and coronary dilatation. Its presence is related to the severity of the condition, even when the cardiological manifestations as such are mild.

Joseph and Abrams in their study "Factors linked to severe outcomes in multisystem syndrome in children (MIS-C) in the USA: a retrospective surveillance study" report that patients with an increased troponin value of 1.0 ng/mL (normal reference 0.04) could have at least a 3-fold increased risk of shock, increasing to 5.5 times with a value of 5.0 ng/mL. In the clinical variables, it stands out that the symptomatology

Table 3. Cardiological findings in patients with a diagnosis of MIS-C with cardiological compromise

Cardiological Findings	n = 9 (%)
<i>Echocardiogram</i>	
<i>LV systolic dysfunction</i>	
- none	4 (44)
- mild	4 (44)
- moderate	1 (11)
- severe	0
<i>LV Dilation</i>	2 (22)
<i>Pericardial effusion</i>	6 (67)
<i>Regurgitation AV Valve</i>	
- Mitral	4 (44)
- Tricuspid	0
<i>Coronary alteration</i>	
- Dilation	2 (22)
- Hyperrefringene	1 (11)
- Aneurysm	0
<i>ECG</i>	
- normal	4 (44)
- altered	4 (44)
- not observed	1 (11)

n: número de paciente, LV: left ventricle, AV: atrioventricle, ECG: electrocardiogram.

Table 4. Treatment received in patients diagnosed with MIS-C with and without cardiological involvement

	Total de Pacientes (n = 13)	WITH cardiological compromise (n = 9)	WITHOUT cardiological compromise (n = 4)
<i>Treatment n (%)</i>			
- Systemic corticosteroids	12 (92%)	8 (88%)	4 (100%)
- IgIV	12 (92%)	9 (100%)	3 (75%)
- LMWH	11 (85%)	8 (88%)	3 (75%)
- ASA	3 (20%)	2 (22%)	1 (25%)
<i>Evolución clínico</i>			
- MEDIAN days of hospitalization (IQR)	10 (8.5-13.5)	11	8,5
- Admission CPU n (%)	10 (77%)	8 (89%)	2 (50%)
- VAD n (%)	3 (23%)	3	0
- IMV n (%)	2 (15%)	2	0
- Length Stay CUP (IQR)	2 (1-4,5)	3	1
- Death n (%)	0	0	0

n: patient number, IVIg: intravenous immunoglobulin, LMWH: low molecular weight heparin, ASA: acetylsalicylic acid, IQR: Interquartile Range, CPU: critical patient unit, VAD: vasoactive drug, IMV: invasive mechanical ventilation.

that allowed making the clinical diagnosis of MIS-C was non-specific for the cardiological involvement, being more frequent in males and with a mean age of 7.5 years. Regarding the comorbidity variable, the presence of malnutrition by excess and respiratory pathology stood out, with no significant correlation with cardiological involvement.

Important factors in our analysis were the values of ProBNP and Ferritin, which showed an increase with statistical significance ($p < 0.01$ in both cases), unlike inflammatory markers such as D-dimer, C-reactive protein, procalcitonin, fibrinogen, LDH, and albumin, which, although they played a role at the time of diagnosis, their degree of alteration was not greater in patients with cardiac involvement versus those without involvement. Leukocytosis and lymphopenia were not statistically relevant. Platelet alteration was not significant as reported in the literature, although a $p = 0.05$ was obtained, very close to the limit of statistical significance, which makes us think that with a higher N, it could reach a significantly important value, as reported in other reports³.

Another point is the low range of lactate alteration in all patients in the series (with and without cardiologic involvement), with a mean value of 14.7 ± 4.6 . A case-by-case analysis showed that, regardless of cardiologic involvement, in the context of a little-known disease and to provide timely treatment, patients were admitted early to a more complex unit, favoring timely hemodynamic management.

When analyzing the results of the laboratory mark-

ers of cardiac involvement, ProBNP was increased in both WCI and WNCI groups, with a value 7.5 times higher in WCI patients than in WNCI patients. In relation to the increase in Troponin I, there was a statistically significant increase in WCI patients compared with those WNCI.

In our casuistry, the findings in the ECG and echocardiogram were transient, with transient repolarization alterations and pericardial effusion being the most frequent. There was only one patient who presented transient first-degree atrioventricular block, evolving with mild symptoms, as reported in the literature.

Regarding the number of days of hospitalization in the ICU, there were no differences between children with or without cardiologic involvement, a situation that could have the bias of considering as more complex a disease of recent onset, without well-known prognostic factors, which explains the preference for management in the ICU during the first hours after the diagnosis was made.

The management of patients was guided by the in-hospital clinical protocol, highlighting the similarity in the therapeutic approach with other inflammatory and immunological pathologies such as Kawasaki disease and other immunological diseases (MAS), the therapy was safe and effective, and no adverse events were reported. Likewise, 2 patients required ASA because they presented Kawasaki phenotype and 3 patients with cardiologic involvement were treated with VAD due to hypotension. Stay in the ICU was brief and with a favorable evolution and then were transferred to

a less complex unit. They received adequate and timely management, which is reflected in the outcomes.

We emphasize that there were no deaths or patients that required ECMO assistance, as has been exceptionally described in the literature¹⁶.

Limitations of the study

It is important to note that these results have the respective limitations of a case study with a small number of patients, in the context of an emerging and initially poorly understood disease.

The study of the troponin marker with two different laboratories, measuring troponin I and troponin uI, which is evaluated with the number of maximum times reference value, a useful value but that could generate some bias in the results. No patient follow-up was performed in this study. The evolution of this disease in the medium and long term remains to be evaluated.

Conclusion

Cardiological involvement in children diagnosed with MIS-C is frequent, most of them show mild to moderate presentation with complete recovery of inflammatory parameters in a short period, similar to what is described in the literature; severe patients were a small number, all with hemodynamic compromise and rapid resolution. Our series shows a favorable evolution with varied and non-specific symptomatology. The markers of cardiologic involvement were increased troponin, proBNP, ferritin, and thrombocytopenia. The most frequent ultrasound finding was pericardial effusion. This allows us to suggest that the management of these patients should be carried out in a hospital of greater complexity and with the availability of cardiological evaluation.

It remains to define the medium- and long-term evolution of this disease in the world and Chile, as well

as to evaluate the findings observed since we do not have enough published data and the natural history of the untreated disease is unknown.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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