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ORIGINAL ARTICLE

Kawasaki disease versus Multisystem Inflammatory Syndrome Covid-19 with Kawasaki disease phenotype

Enfermedad de Kawasaki versus Síndrome Inflamatorio Multisistémico Covid-19 con fenotipo enfermedad de Kawasaki

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

Pediatric Inflammatory Multisystem Syndrome (PIMS) has been described in numerous publications. In Chile, there is local research related to this topic, although to date there have been no comparative studies between PIMS and Kawasaki disease. This means that, although there is scattered information on both conditions separately, a complete understanding of how they are related and differ in the Chilean population is still lacking.

What does this study contribute to what is already known?

Through the comparison between both groups, our work contributes to the knowledge and understanding of the clinical, laboratory, and evolutionary similarities and differences between Kawasaki disease (KD) and the PIMS-KD phenotype in the Chilean population. This knowledge is essential for physicians caring for pediatric patients since there is currently no specific diagnostic test for KD or PIMS-KD. Our study provides a solid basis for improving diagnostic suspicion and differentiation between these two clinical entities, which may have a significant impact on the care and treatment of these patients in Chile.

Abstract

In pediatrics, a process called Pediatric Inflammatory Multisystem Syndrome (PIMS) associated with recent infection by SARS-CoV-2 virus has been observed. One of its variants presents similarities with Kawasaki disease (KD). **Objective:** to compare the clinical presentation, laboratory testing, and evolution of KD with PIMS Kawasaki phenotype (PIMS-KD) in patients hospitalized before the pandemic, compared with the pandemic period. **Patients and Method:** Cross-sectional study in two groups of patients at the *Hospital Exequiel González Cortés*: typical KD (group 1) and PIMS-KD

Keywords:
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(group 2). Data on demographic, clinical, and biochemical details were collected, as well as echocardiogram, treatment, and evolution records. IgG and IgM serology for SARS-CoV-2 was performed in both groups. **Results:** In the KD group and the PIMS-KD group, 20 and 33 patients were analyzed, respectively. There were differences in age, days of fever, count of leukocytes, lymphocytes, and platelets, erythrocyte sedimentation rate (ESR), and hospital stay. In 25% of the KD group, there were alterations in the echocardiogram and, in the PIMS-K group, all patients received corticosteroids and 25 patients received intravenous immunoglobulin (IVIG). In both groups, a favorable clinical evolution was observed, characterized by the absence of complications and mortality. **Conclusions:** Based on the data obtained in our study, the importance of the epidemiological link is emphasized as an essential factor in differentiating between both pathologies, highlighting the need to consider factors such as age, duration of fever, count of leukocytes, lymphocytes, and platelets, and degree of cardiac involvement, for a differential evaluation between patients with PIMS-KD versus KD.

Introduction

In December 2019, several cases of pneumonia were reported in Wuhan, China related to a new virus that was identified on January 07, 2020, as nCOV-2019 and on February 11, 2020, became known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) and the disease caused by the virus as Coronavirus Disease 19 (COVID-19). On March 11, the World Health Organization (WHO) declared the disease a global pandemic. In Chile, the first case was reported on March 3, 2020.

Most symptomatic COVID-19 cases occur in the adult population, with a clinical picture similar to influenza that can be mild to severe cases requiring hospitalization, with severe interstitial pneumonia with activation of the inflammatory cascade and a mortality rate of 2 to 3% approximately.

In children, SARS CoV-2 infection is generally mild and benign; however, a severe inflammatory entity has been described in the pediatric population, which would be related to SARS CoV-2 infection, called the Pediatric Inflammatory Multisystem Syndrome (PIMS), which shares common clinical features with other known pediatric conditions such as Kawasaki disease (KD), toxic shock, septic shock, and macrophage activation syndrome. The first cases were reported in 2020 in Italy, the United Kingdom, France, and the United States. On May 4, 2020, the Centers for Disease Control and Prevention (CDC) defined the diagnostic criteria and on May 15, 2020, the WHO made a preliminary case definition.

Current evidence suggests that the damage caused by SARS CoV-2 infection is mainly mediated by activation of the immune system, generating a cytokine storm that gives rise to the clinical features of this syndrome.

Kawasaki disease (KD) is a multisystem vasculitis that involves medium-sized vessels including the coronary arteries; it is one of the main causes of acquired heart disease in pediatric patients in developed countries. Its etiology is unknown and the clinical picture is acute, involving multiple organs. The clinical diagnosis is based on several criteria, which have been modified over time, the most current being those of the Kawasaki Disease Research Committee Guidelines and the American Heart Association updated in 2017. Cases of incomplete or atypical KD have also been described[4].

The objective of this study was to compare the clinical presentation, laboratory tests, and outcome of patients hospitalized with a diagnosis of KD before the pandemic with patients with PIMS Kawasaki disease phenotype (PIMS-KD) during the pandemic.

Patients and Method

Study design

A cross-sectional study was performed, in which 2 groups were defined: Typical KD (group 1) and PIMS-KD [group 2 in patients admitted to the *Hospital Dr. Exequiel González Cortés* (HEGC)]. Clinical records of both groups were reviewed according to discharge diagnosis, either KD or PIMS. Demographic and clinical data, treatment and evolution, history of contact with confirmed or suspected COVID-19 cases, as well as laboratory parameters and echocardiographic findings were collected. All data were recorded in an Excel® spreadsheet with strict confidentiality.

The study was approved by the ethics committee of the South Metropolitan Health Service and by the Teaching and Research Unit of the HEGC.

Inclusion criteria

For group 1, typical KD cases hospitalized at the HEGC, who met criteria according to the American Heart Association 2017[19] between January 01, 2016,

to December 31, 2019, were selected. For group 2, PIMS-KD cases hospitalized at the same center and meeting WHO criteria[4] between April 01 to December 31, 2020, were selected. Each of these groups consisted of the entire population available for the established diagnoses and meeting the previously defined criteria.

Exclusion criteria

In group 1, patients with atypical or incomplete KD, another cause of fever, and patients with chronic pathologies were excluded while in group 2, patients with a diagnosis of COVID-19 who did not meet PIMS-KD criteria or in whom a cause for the inflammatory picture was identified were excluded.

Variables to be studied and measuring system

Demographic variables (sex and age), clinical picture (fever, conjunctival injection, edema, desquamation of the limbs, lymphadenopathy, abdominal pain, vomiting, diarrhea, and shock), laboratory values (CBC, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), transaminases, and biochemical profile), echocardiogram findings, hospital evolution (admission unit, days of hospital stay, and lethality), treatment (mechanical ventilation (MV) support, use of vasoactive drugs (VAD), use of antibiotics, intravenous immunoglobulin (IVIG), systemic corticosteroids, antiplatelet agents, and anticoagulation), epidemiological contact with a confirmed or suspected COVID-19 case, and anti-SARS CoV-2 antibodies (IgM and IgG) in plasma samples, by electrochemiluminescent immunoassay (ECLIA) for total anti-SARS-CoV-2 immunoglobulin, using the Elecsys® immunoassay with the Cobas e 411 platform analyzer (Roche Diagnostics). The positivity of this test was considered compatible with previous exposure to SARS-CoV-2. It should be noted that the study was performed before the incorporation of the anti-SARS-CoV-2 vaccine in this age group.

Statistical analysis

The statistical analysis was based on descriptive statistics. For quantitative variables, mean and median were calculated, expressed as standard deviation (SD) and interquartile range (IQR), respectively, and qualitative variables were presented as percentages. A comparison between groups was performed using the Student's t-test, the Mann-Whitney U test for unpaired samples, and the contingency test for categorical variables. A $p \leq 0.05$ was considered significant. Data distribution and statistical analysis were performed using the GraphPad Prism 8.3.0 software.

Results

During the period between January 2016 and December 2019, 23 patients with KD were diagnosed, of which 3 were excluded since they did not meet inclusion criteria (2 of them with incomplete KD diagnosis and 1 of them due to presenting KD flare-up, only the 1st episode was considered), resulting in a final group of 20 patients. During the observation period, 37 PIMS cases were diagnosed, of which 4 were excluded because they did not meet the WHO criteria for KD phenotype. Table 1 shows the demographic characteristics of both groups. In relation to the age of the patients, it was found that the median in group 1 was 3 years, while for group 2 it was 5.4 years, which represents a significant difference. No significant differences in sex were observed in either group.

Table 2 shows the clinical manifestations in both groups. The mean number of days of fever before admission in group 1 was 7 days, while in group 2 it was 3.9 days, which was statistically significant.

In relation to other symptoms and signs explored, there were statistically significant differences in conjunctival injection (95% vs. 48.4%) and adenopathies (85% vs. 12.1%), which were higher in group 1. On the other hand, in group 2, a higher prevalence of abdominal pain (13.3% vs. 86.6%) and shock symptoms (5% vs. 54.5%) was observed.

Complementary tests

Table 3 shows the results of laboratory tests. The main differences between the two groups were observed in the CBC. In group 1, a higher WBC count was observed, with a mean of 16.84 K/uL compared with group 2 which showed a mean of 11.57 K/uL, which is a statistically significant difference. In addition, when analyzing the differential leukocyte formula, a significantly lower absolute lymphocyte count was observed in group 2, with a mean of 1.37 K/uL, compared with group 1, which showed a mean of 3.9 K/uL.

A higher value of HSV was found in group 1 with a mean of 69.5 mm/hr, compared with a mean of 43 mm/hr in group 2. No significant differences were identified in the other parameters analyzed.

20 echocardiograms were performed in group 1 and 31 in group 2. In group 2, the presence of hyperreflection predominated (0% vs. 27.2%; $p < 0.05$). The presence of aneurysms was observed in both groups, showing no differences.

Management

In group 1, 17.2% (n: 5) were admitted to the Critical Patient Unit (CPU) versus 72.7% (n: 24) of group 2, which constitutes a significant difference. Table 5

Table 1. Comparison of demographic data between Kawasaki Disease (group 1) and PIMS – Kawasaki phenotype (group 2)

	Group 1 (n: 20)		Group 2 (n: 33)		
Gender	n	Percentage (%)	n	Percentage (%)	P-value
Males	11	55%	18	54.5%	> 0.99
Females	9	45%	15	45.4%	
Age (years)	Median	IQR [1.3 - 4.0]	Median 5.4	IQR [2.6 - 8.4]	< 0.05

IQR: Interquartile range. PIMS: Pediatric inflammatory multisystem Syndrome.

Table 2. Comparison of clinical features at admission between Kawasaki Disease (group 1) and PIMS – Kawasaki phenotype (group 2)

	Group 1 (n: 20)		Group 2 (n: 33)		
	Median	IQR	Median	IQR	P-value
Fever (days)	6	[4.2 - 8.7]	3	[2.0 - 5.0]	< 0.05
Temperature (°C)	39.5	[39 - 39.8]	39	[39 - 40]	0.15
Clinical features	n	Percentage (%)	n	Percentage (%)	P-value
Rash	19	95	21	70%	0.09
Conjunctival injection	19	95	16	48.40%	< 0.05
Edema	11	55	13	39.30%	0.39
Palm and sole desquamation	8	40	3	9.09%	< 0.05
Lymphadenopathy	17	85	4	12.10%	< 0.05
Abdominal pain	4	13.3	26	86.60%	< 0.05
Vomiting	8	40	15	45.40%	0.77
Diarrhea	9	45	12	57.10%	0.76
Shock	1	5	18	54.50%	< 0.05

PIMS: Pediatric inflammatory multisystem Syndrome.

Table 3. Comparison of laboratory features between Kawasaki Disease (group 1) and PIMS – Kawasaki phenotype (group 2)

	Group 1 (n: 20)		Group 2 (n: 33)		
	Median	Percentage (%)	Median	Percentage (%)	p
Hemoglobin (g/dL)	11.09	0.91	10.7	1.69	0.62
	Median	SD	Median	SD	p
Leukocyte count (K/uL)	16.847	7.223	11.578	5.336	< 0.05
Lymphocytes (K/uL)	3.9	1.882	1.375	859	< 0.05
Platelets (K/L)	268	140.760	212.818	85.508	< 0.05
Erythrocyte sedimentation rate (mm/hr)	69.41	27.82	37.43	29.9	< 0.05
C-reactive protein (mg/L)	106	64.84	153.6	116	0.38
SGOT (U/L)	37.13	17.87	41.26	26.16	0.9
SGPT (U/L)	47.58	42.8	37.13	17.87	0.18
GGT (U/L)	90.06	58.53	73.76	108.3	0.06
ALP (U/L)	224.8	72.11	177.4	70.38	< 0.05
Total bilirrubin (mg/dL)	0.76	1.8	0.8	1.0	0.48
Serum creatinine (mg/dL)	0.32	0.15	0.4	0.16	0.06

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; ALP: alkaline phosphatase; PIMS: Pediatric inflammatory multisystem Syndrome.

Table 4. Comparison of echocardiographics findings between Kawasaki Disease (group 1) and PIMS – Kawasaki phenotype (group 2)

	Group 1 (n: 20)		Group 2 (n: 33)		
	n	Percentage (%)	n	Percentage (%)	P-value
Normal coronaries	15	68.1	16	48.4	0.17
Hyperrefringency	0	0	9	27.2	< 0.05
Coronary artey dilatation	3	13.6	3	9.0	0.67
Coronary artery aneurysms	1	4.5	1	3.0	> 0.99
Pericardial effusion	1	4.5	2	6.0	> 0.99

PIMS: Pediatric inflammatory multisystem Syndrome.

Table 5. Comparison of clinical evolution and treatment between Kawasaki Disease (group 1) and PIMS – Kawasaki phenotype (group 2)

	Group 1 (n: 20)		Group 2 (n: 33)		
	n	Percentage (%)	n	Percentage (%)	P-value
PICU	5	17.2	23	71.4	< 0.05
Mechanical ventilation	1	5	15	45.4	< 0.05
Vasoactives drugs	1	5	17	51.5	< 0.05
Corticosteroids	3	15	28	84.8	< 0.05
IVIG	20	100	25	75.6	< 0.05
Acetyl salicylic acid	20	100	26	78.7	< 0.05
Light molecular weight heparin	1	5	22	66.6	< 0.05
Antibiotics	6	30	32	96.9	< 0.05
Death	0	0	0	0	0
	Median	IQR	Median	IQR	P-value
Length of stay in PICU	2	[1.0 - 4.0]	4	[1.3 - 4.0]	0.05
Length of stay	6	[4.0 - 8.0]	9	[7.0 - 10.5]	< 0.05

PICU: Pediatric unit critical care; IVIG: Intravenous immunoglobulin; PIMS: Pediatric inflammatory multisystem Syndrome.

shows the MV requirements, VAD, and treatments received in both groups. There were significant differences in the management of group 2, requiring greater admission to the CPU, use of MV, VAD, and a median hospital stay of 9 days vs. 6 days in group 1. There were no deaths in either group.

Discussion

According to studies, the incidence of COVID-19 disease in children is significantly lower compared to that in adults. In most cases, the indication for hospitalization in pediatric patients with COVID-19 infection is mainly due to the development of Respiratory Distress Syndrome, with a mortality rate close to zero.

PIMS-KD is a severe and potentially life-threatening entity, which constitutes a challenge for diagnosis and management given its similarity to other pediatric pathologies[12]. The epidemiological link is essential for the diagnosis of PIMS-KD, which agrees with our study. KD still has no known cause; one hypothesis proposes that there is an inadequate immune system response to pathogens in genetically predisposed patients.

The days of CPU stay required also differ in both clinical entities, being higher in PIMS-KD. Likewise, the total duration of hospitalization presents a significant difference, being higher in the PIMS-KD group, with a median of 9 days. This finding is consistent with

data reported in the international literature, which suggest a median duration of 7 days.

According to our results, the age of the patients was lower in patients with KD compared with patients with PIMS-KD and was higher in male patients but without a statistically significant difference, which is consistent with international publications. The days of fever were lower in patients with PIMS-KD, although we cannot compare with international studies since most of them do not differentiate between both clinical entities[28].

Laboratory tests in both groups were characterized by an increase in acute phase reactants. In addition, lymphopenia was more frequent in the PIMS-KD group, which coincides with that described in the literature with a mean of 1.37 K/uL, ranging from 0.5 to 1.5 K/uL[21]. Ferritin, D-dimer, and fibrinogen values were abnormal in hospitalized patients with diagnosis of PIMS-KD but could not be compared with the KD group since they are not clinical parameters used for KD diagnosis.

Although cardiac involvement was indeed present in both groups, in our study, it was observed that the PIMS-KD group presented greater cardiac involvement, with coronary artery ectasia and hyperreflection as the most frequent findings. The presence of shock in patients with PIMS-KD as described in the literature ranges between 40-80%, similar to our findings (51.5%).

Regarding treatment in KD, there is consensus on the use of IVIG (2 gr/kg) within 10 days after symptom onset and acetylsalicylic acid (ASA), however, about 15% of patients show resistance to IVIG, requiring additional doses and/or the use of systemic corticosteroids[31].

At the beginning of the presentation of patients with a diagnosis of PIMS-KD, there were no international recommendations for the treatment of these patients, so in the first cases, therapy was based on the use of IVIG, corticosteroids, and ASA was administered similarly in both groups. Currently, in our hospital and at the national level, there is a protocol according to clinical presentation which is similar to other publications[xxxix]. Most of the patients in group 2 were admitted to the CPU, probably due to the severity of the condition and lack of knowledge of the disease.

Currently, in Chile, there are no comparative studies that help to differentiate between PIMS-KD and typical KD. Our research represents one of the first attempts to compare both groups and we believe it constitutes a valuable contribution for physicians caring for pediatric patients. Importantly, there are no specific diagnostic tests for either KD or PIMS-KD at present, which possibly led to the inclusion of some KD patients in the PIMS-KD group in our study. The epidemiological link played a key role in our diagnostic suspicions and the differentiation between the two clinical entities.

Unfortunately, the retrospective design of this study represents a limitation. In addition, the restriction in the number of patients is another limitation that makes it difficult to establish associations between several variables. Therefore, it is crucial to carry out future studies, preferably multicenter ones, that address both groups, in order to broaden our understanding and obtain more robust results.

Conclusions

KD and PIMS-KD were compared in pediatric patients. The results highlight the importance of the epidemiological link to differentiate both pathologies, underlining the need to consider factors such as age, fever duration, and laboratory parameters for accurate assessment. The study showed significant differences in clinical presentation, laboratory tests, and management between the two groups. The PIMS-KD group presented greater cardiac involvement and a higher risk of admission to the CPU. Despite limitations, such as the lack of specific diagnostic tests, this research contributes to the understanding of these clinical entities in the Chilean pediatric context. It highlights the need for future multicenter studies to obtain more robust results and improve the understanding of these pathologies.

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.

Financial Disclosure

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