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Clinical characteristics and course of patients with Kawasaki disease at a general hospital

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ABSTRACT

Kawasaki disease (KD) is considered the leading cause of acquired heart disease in children younger than 5 years. Our objective was to know the clinical characteristics, coronary involvement, and course of patients seen at our facility.

A case series from 2001 to 2018 was reviewed. Sixty-three patients were included; their median age was 2.6 years; 58% were males. The median duration of fever at the time of diagnosis was 5.5 days.

The incomplete form was observed in 33% and coronary involvement, in 20%. Among patients with coronary involvement, 60% had incomplete KD versus 28% among those without coronary involvement (*p:* 0.06). No differences were observed between groups in laboratory data based on coronary involvement. To conclude, 33% had incomplete KD and 20%, coronary involvement. There was a trend to a higher risk for coronary artery damage in the incomplete form of KD.

Key words: *Kawasaki disease, classification, intravenous immunoglobulins, coronary artery aneurysm.*

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INTRODUCTION

Kawasaki disease (KD) is a self-limited systemic vasculitis that involves small- and medium-caliber vessels. It occurs mainly in children younger than 5 years and is the leading cause of acquired heart disease; it is diagnosed based on clinical criteria.[1,2]

KD incidence varies: Japan reports 308 cases per year per 100 000 children under 5 years of age; the United States, 20; and Europe, between 5 and 15.[3,4] There are no data about the annual incidence of KD in Argentina, although Urrutia has estimated it is 4 cases per 100 000 consultations.[5]

Coronary involvement occurs in 15-25% of untreated patients and decreases to 4-8% when patients receive gamma globulin treatment.[6,7] It is the determining factor of morbidity and mortality, so it is important to identify risk factors.[8]

Different risk factors have been proposed, including age younger than 36 months, fever for at least 6 days, incomplete form of KD, erythrocyte sedimentation rate (ESR) above 50 mm/h, C-reactive protein (CRP) above 100 mg/L, hematocrit below 30%, leukocytosis above 20 000/mm^3, and thrombocytosis a week after diagnosis, among others.[9–11] In Argentina, the studies by Schroh and Melonari reported coronary involvement in 16% of cases and the same risk factors mentioned above.[12,13]

There are few publications in Argentina on KD. Therefore, our objective was to describe the clinical characteristics, coronary involvement, and course of patients with KD seen at a community teaching hospital.

POPULATION AND METHODS

A case series of patients with KD was reviewed. Children younger than 18 years hospitalized with a recent diagnosis of KD or referred for KD management between 2001 and 2018 were included. Patients who were treated and followed by the cardiac and rheumatology services at a different facility were excluded.

KD was identified in electronic medical records, and each was reviewed manually.

The following variables were analyzed: age, sex, ethnicity, clinical characteristics at the time of diagnosis. ESR, CRP, leukocyte count, hemoglobin, hematocrit, and platelet count at the time of diagnosis, 1 week and 1 month after starting treatment with the first dose of gamma globulin were also analyzed.

Echocardiographic findings were recorded at the time of diagnosis and during follow-up. Echocardiographic findings were defined as abnormal according to the body surface area Z-score tables proposed by the American Heart Association.[2] Coronary involvement was defined as the presence of ectasia, aneurysm or qualitative alterations.

Regarding treatment, days of fever before gamma globulin infusion, requirement of a second dose, recurrence of fever, and other treatments administered were recorded.

Supplementary material 1 describes KD diagnostic criteria and *Supplementary material 2* shows the diagnostic algorithm for incomplete KD according to the American Heart Association.[2]

Categorical variables were expressed in absolute numbers and percentage. Continuous variables were described as mean and standard deviation (SD) or median and interquartile range (IQR) 25–75, based on their distribution. The χ^2 test, the Wilcoxon test, and Student's t test were used depending on variables analyzed.

The study was approved by the Ethics Committee for Research Protocols of our site (no. 5258).

RESULTS

Seventy-two patients were selected; 9 were excluded due to missing data or different

Table 1. Clinical characteristics of patients with Kawasaki disease (n = 63)

Age, years, median (IQR 25–75)	2.6	(1.3–3.6)
Males, n (%)	37	(58.7)
Days of fever at the time of diagnosis, median (IQR 25–75)	5.5	(5–8)
Mucosal involvement, n (%)	36	(57)
Conjunctivitis, n (%)	31	(49)
Rash, n (%)	36	(57)
Involvement of hands and feet, n (%)	19	(30)
Lymphadenopathy, n (%)	18	(28)

IQR: interquartile range; n: number.

diagnosis. A total of 63 patients diagnosed with KD were included.

There was no patient of Asian ethnicity; 58% of patients were males; patients' median age was 2.6 years (IQR: 1.3–3.6). The median duration of fever at the time of diagnosis was 5.5 days (IQR: 5–8).

The clinical characteristics at the time of diagnosis are shown in *Table 1*. *Table 2* describes laboratory parameters at the time of diagnosis, at 1 week, and at 1 month.

Incomplete KD was observed in 33% (17/52), with a median duration of fever at the time of diagnosis of 7.5 days (IQR: 5–10).

Coronary involvement was present in 20% of patients (11/55) for whom data on cardiac assessment was available.

Coronary involvement was observed in 11% of patients (4/35) with complete KD and in 35% of patients (6/17) with incomplete KD.

Age was not significantly associated with incomplete KD or coronary involvement.

The incomplete form of KD occurred in 6/10 patients with coronary involvement versus 11/39 patients without coronary involvement (p 0.06). The highest CRP levels, both in patients with and without coronary involvement, were observed in those who did not respond to the initial treatment.

In these patients, the median CRP at diagnosis was 215.6 mg/dL versus 71.8 mg/dL compared to those who responded to a single gamma globulin dose ($p < 0.05$); leukocyte levels were 19 938/mm^3 versus 14 015/mm^3 ($p < 0.01$), respectively. No statistically significant differences were observed in other laboratory data (*Table 3*).

Cardiac follow-up was provided in our facility to 50% of patients (32/63). The median duration of follow-up was 3.6 years (IQR: 1.7–7.5) and of time to resolution of coronary involvement, 2 months (IQR: 1.2–4.4). *Table 4* describes the course of patients' with coronary involvement.

Table 2. Laboratory characteristics of patients with Kawasaki disease

	Before treatment n = 53	7 days after treatment n = 40	30 days after treatment n = 30
ESR mm, median (IQR)	66 (31.5–77.5)	58 (43–83)	16 (10.5–24)
CRP mg/dL, median (IQR)	73.3 (24.4–142.6)	8 (3.2–27.7)	0.35 (0.2–1)
Leukocytes cells/mm^3, mean (SD)	14 937 (6191)	10 690 (6559)	9195 (2528)
Hematocrit %, mean (SD)	31.9 (3.1)	31.9 (3.7)	34.5 (2.8)
Hemoglobin g/dL, mean (SD)	10.9 (1)	11 (1.3)	11.9 (1.1)
Platelets cells/mm^3, mean (SD)	351 800 (152 263)	619 950 (182 155)	356 600 (106 780)

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SD: standard deviation; IQR: interquartile range.

Table 3. Clinical and laboratory characteristics of patients with Kawasaki disease based on coronary involvement

	Without coronary involvement n = 44	With coronary involvement n = 11	*p*-value
Males, n (%)	25 (56.8)	7 (63.6)	NS*
Age years old, median (IQR)	2.5 (1.5–3.5)	3 (1.9–3.7)	NS**
Days of fever at the time of diagnosis, median (IQR)	5 (5–8)	6 (5–9)	NS**
Maximum erythrocyte sedimentation rate mm, median (IQR)	66 (44–81)	31 (19–58.5)	NS**
Maximum C-reactive protein mg/dL, median (IQR)	73.8 (34.4–142.6)	24.4 (15.3–77.4)	NS**
Maximum leukocytes cells/mm^3, mean (SD)	14 210 (6768)	13 430 (4147)	NS***
Minimum hematocrit %, mean (SD)	32.6 (2.5)	31.5 (4.5)	NS***
Minimum hemoglobin g/dL, mean (SD)	10.9 (0.9)	10.6 (1.6)	NS***
Maximum platelets cells/mm^3, mean (SD)	348 350 (131 245)	337 000 (225 167)	NS***

**χ^2 test.*
***Wilcoxon test.*
****Student's t test.*
SD: standard deviation; IQR: interquartile range.

All patients received initial treatment with gamma globulin (2 g/kg) and anti-inflammatory doses of aspirin. Ten patients were considered non-responders because they had persistent fever and received a second dose of gamma globulin. Three of these patients had coronary involvement: 2 received intravenous glucocorticoids, and 1 also received infliximab.

DISCUSSION

There are few studies in Argentina that describe the clinical characteristics and course of patients with KD. In our study, the median age at diagnosis was 2.6 years, similar to that described in a multicenter study of 625 patients conducted in Spain, where the median age was 2.8 years.[14] The male/female ratio was 1.4/1, similar to the 1.3/1 ratio observed in Japan.[3] The median duration of fever at the time of diagnosis was 5.5 days, so it can be inferred that treatment was administered in a timely manner.

The diagnosis of incomplete KD is a challenge due to the lack of defined criteria. KD may be suspected in children with fever for 5 days or more and 2 or 3 compatible clinical criteria or in children with fever for 7 days or more without other explanation and in children with compatible laboratory or echocardiographic findings. In our study, 33% of patients had incomplete KD, which is similar to that observed in Spain (29.5%) and in our country (25% and 38%).[12-14] However, in Japan, the incomplete form of KD is reported in only 19% of cases.[3]

Table 4. Clinical course of patients with coronary involvement

Diagnosis	n	Clinical course
Coronary ectasia	7	6 resolved 1 no data
Coronary artery aneurysm	3	1 persistent aneurysm 1 resolved 1 no data
Dilated cardiomyopathy and giant coronary artery aneurysms in right and left coronary arteries	1	1 in heart transplant waiting list*

**The diagnosis of Kawasaki disease in this patient was delayed and retrospective.*

Coronary involvement was observed in 20% of patients. Although this value is similar to the series without treatment, it is possible that some of the patients may have been referred after a longer course than that mentioned, that our hospital receives patients referred from other centers for cardiac follow-up due to coronary involvement, and that the pediatric cardiologists working here have a high level of training in the diagnosis of coronary artery alterations.

Manifestations included coronary ectasia, coronary artery aneurysm, and giant coronary artery aneurysm. In Spain, 23% of patients had coronary artery lesions, similar to what has been reported in our study.[14] Conversely, in Japan, 4.2–8.5% of patients with KD had coronary lesions; however, it is difficult to compare this population with that of Western countries given the high prevalence and suspicion rate of KD in that country.[3]

Although many publications have described the risk factors for coronary involvement, published studies have shown varying results. In this study, slightly more than half of the patients who developed coronary involvement had incomplete KD, a risk factor described in the bibliography about coronary artery involvement.[9,15] In addition, although no differences were observed when assessing the risk factors associated with coronary involvement, we believe that this could be due to the limited number of patients.

Since the frequency of KD is very low in the West, most published studies, such as this one, have an observational and retrospective nature. We believe that this is the main limitation of this study, in addition to the fact that it was carried out in a single site and that data were collected from the electronic medical records.

Although this study has limitations, it provides information on the clinical characteristics, course, and coronary involvement of patients with KD in Argentina.

CONCLUSIONS

Incomplete KD was observed in 33% of patients, and coronary involvement was observed in 20%. There was a trend to a higher risk for coronary artery damage in the incomplete form of KD. ■

Supplementary material available at: https://www.sap.org.ar/docs/publicaciones/archivosarg/2023/2364_RC_Geli_Anexo.pdf

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