Risk of coronary artery involvement in Kawasaki disease

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ABSTRACT

Introduction: Kawasaki disease refers to systemic vasculitis with risk of coronary artery disease. Our objective is to identify risk factors associated with coronary artery disease in patients with complete and incomplete Kawasaki disease.

Material and methods: Descriptive, retrospective study conducted in patients diagnosed with Kawasaki disease in a tertiary-care hospital between 2008 and 2014. The American Heart Association diagnostic criteria were used to define complete and incomplete Kawasaki disease.

Results: Thirty-one children were diagnosed with Kawasaki disease; 24 met the criteria for the complete form, and 7, for the incomplete form of this condition. Five had coronary artery disease. One of them had incomplete Kawasaki disease (1/7= 14.3%), and the remaining four had the complete form (4/24= 16.7%). No significant differences were found between both groups (*p*= 1.0). Patients with coronary artery involvement had a higher C-reactive protein level (median: 16.2 mg/dL versus 8.4 mg/dL, *p*= 0.047) and lower albuminemia (median: 3.2 mg/dL versus 3.99 mg/dL, *p*= 0.002).

Conclusions: The risk of coronary artery involvement in incomplete Kawasaki disease is similar to that in complete Kawasaki disease; therefore, in patients with the incomplete form, immunoglobulin therapy should not be delayed. In our population, C-reactive protein and albumin levels were related to a higher risk of coronary artery involvement.

Key words: Kawasaki disease, risk factors, coronary artery disease.

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INTRODUCTION

Kawasaki disease (KD), described by Tomisaku Kawasaki in 1967, is a systemic vasculitis of unknown etiology that involves small- and medium-caliber vessels. It is an acute, self-limited inflammatory but potentially severe process because of the heart complications that might occur.[1] Although KD is more frequent in Asian countries, especially in Japan, with an annual incidence of 239.6/100 000 children younger than 5 years old, the distribution pattern of the disease is universal and can be found in children of any ethnic group.[2] In the United States, KD has an overall hospitalization rate of 17.1/100 000 children. In Europe, some studies have established KD incidence to be between 4.9/100 000 children younger than 5 years old in Denmark and 9/100 000 children in France.[2]

The prognosis of the disease depends on the degree of coronary artery disease (CAD). Up to 15-25% of untreated patients have CAD. Such percentage decreases to less than 5% in patients receiving gammaglobulin treatment before day 10 of the disease.[1,3] Currently, KD is considered the main cause of acquired heart disease during childhood in developed countries.[3,4] Incomplete KD has been related to a greater delay in diagnosis and treatment onset, which, in turn, could result in a higher CAD risk.[5,6]

Our objective is to identify risk factors associated with coronary artery disease in patients with complete and incomplete KD.

MATERIAL AND METHODS

A retrospective, descriptive study has been performed in which medical records of children younger than 18 years old, diagnosed with KD, have been collected in a tertiary care hospital, between January 2008 and December 2014.

KD diagnosis in its complete and incomplete form was established according to the criteria defined by the American Heart Association (AHA).[7] Complete KD diagnostic

criteria were fever persisting at least 5 days and the presence of at least 4 of the following 5 criteria: (1) changes in limbs: erythema of the palms and soles or swelling of the hand and feet in the acute phase and/or fingers and toes periungual desquamation in the subacute phase; (2) polymorphous exanthema; (3) bilateral non-exudative conjunctival injection; (4) changes in lips and oral cavity: erythema and cracking of lips, strawberry tongue and pharyngeal hyperemia; (5) cervical lymph node enlargement (>1.5 cm in diameter), excluding other diseases with similar clinical features. Incomplete KD diagnostic criteria were the following:[7] fever of, at least, 5 days long and the presence of 2 or 3 of the previously mentioned clinical criteria of the disease, together with C-reactive protein (CRP) ≥3 mg/dL and/or erythrocyte sedimentation rate (ESR) ≥40 mm/h and, at least, 3 of the following analytical abnormalities: albumin ≤3 g/dL, anemia for the age, increased level of the glutamic pyruvic transaminase (GPT), platelet level after day 7 ≥450 000/mm³, total leukocytes ≥15 000/mm³ and pyuria ≥10 leukocytes/high power field. The first day of the disease was defined as the first day with a body temperature ≥38 °C.

The standard treatment was that recommended by the American Academy of Pediatrics[7] consensus that consists of the administration of an IV gammaglobulin dose (2 g/kg) combined with acetylsalicylic acid (ASA) in anti-inflammatory doses (80-100 mg/kg) up to 48-72 hours after the fever had stopped and CRP levels had normalized, to continue with ASA in antiplatelet dose (3-5 mg/kg), at least during 2 weeks, and if there are coronary artery abnormalities, until they are no longer present.

An echocardiography was done within the first 48 hours after the diagnosis of complete or incomplete KD. According to the study group of KD of the AHA,[7] the following grades of risk stratification were considered: (I) no coronary artery changes; (II) transient coronary artery ectasia or dilation that resolved in 6-8 weeks; (III) single aneurysm >3 mm, but <6 mm in ≥1 coronary artery; (IV) ≥1 aneurysm ≥6 mm or multiple aneurysms in the same coronary artery; and (V) coronary artery obstruction observed during angiography. Any dilation ≤3 mm with a Z score >2 was considered coronary ectasia.

The study database was developed using Microsoft Access 2010, and IBM SPSS Statistics 20.0 was used for the statistical analysis.

Quantitative outcome measures were described using the mean and standard deviation (SD), or the median and the interquartile range (IQR) based on the distribution of each outcome measure. Qualitative outcome measures were stated as counts (n) and percentages (%). Quantitative outcome measures were compared by means of the Student's t test if outcome measure distribution met normality criteria, or by the Mann-Whitney test if the distribution was abnormal. Comparisons between the two qualitative outcome measures were done with the χ^2 test. A $p < 0.05$ was considered as the limit of statistical significance.

This study was conducted following the principles of good practices outlined in the Declaration of Helsinki. The hospital Ethics Committee approved the conduction of this study.

RESULTS

During the study period, 35 children were diagnosed with KD; 24 (77.4%) met the criteria for the complete form, and 7 (22.6%), for the incomplete form. Four children were excluded because they did not meet KD (complete or incomplete) diagnostic criteria or they had not been correctly identified in the medical records.

Overall characteristics of the 31 patients included, like gender and age at the time of the diagnosis, can be seen in *Table 1*. Ages of the 5 patients with CAD were 3.2, 5.6, 6.8, 12.1 and 58.3 months old. The median age of this group of patients was 6.8 months old (IQR: 4.4-35.2).

Of all cases, 32.2% occurred in winter; 25.8%, in summer; 22.6%, in spring; and 19.3%, in autumn. The median number of visits to the Emergency Department prior to the diagnosis was 1.00 (IQR: 1-3). Eighteen (58.1%) patients had received antibiotic treatment prior to KD diagnosis due to suspected bacterial disease.

Clinical manifestations and laboratory findings

Clinical manifestations that patients had at the time of KD diagnosis are described in *Table 1*. Together with KD diagnostic criteria, it is worth pointing out that 3 patients had liver enlargement and 1, gallbladder hydrops. Irritability was especially present in younger patients. In short, 75% of children under 2 years old, and 100% of those under 1 year old had this symptom as a characteristic finding. Sterile pyuria was detected in 9 cases (29%). Regarding the main clinical differences between incomplete and complete KD, we have found that in the 7

patients with incomplete KD, the most common findings were periungual desquamation and gastrointestinal symptoms, both present in 5 of the patients. Changes in the limbs, like erythema and/or edema, and the presence of lymph node enlargement >1.5 cm were only present in 2 of the 7 children with incomplete KD. Analytical values at the time of KD diagnosis are shown in *Table 2*.

TABLE 1. *General characteristics and clinical manifestations at the time of diagnosis*

	Absolute number	Frequency (%)
General characteristics		
Sex (male); n (%)	19	61.3
Age in months old; median (IQR)	18	12.2-40.3
Younger than 5 years old; n (%)	27	87
Younger than 1 year old; n (%)	7	22.6
Fever ≥5 days*		
Mean duration: 7.71 (5-25); SD: 4.82		
Median: 1 (IQR: 1-3)	31	100
Mean maximum temperature: 39.5 °C; SD: 0.5		
Lymph node enlargement (>1.5 cm)*	17	58.7
Left	5	29.4
Right	10	58.8
Bilateral	2	11.8
Rash*	28	90.3
Maculopapular	6	21.4
Scarlatiniform	14	50
Urticarial	2	7.1
Others (except petechiae or vesiculobullous disease)	6	21.4
Conjunctival hyperemia without discharge*	28	90.3
Lip/oral cavity involvement*	29	93.5
Redness/cracking of the lips	26	100
Strawberry tongue	18	78.3
Pharyngeal hyperemia	24	77.4
Changes in limbs*	26	89.7
Acute phase:	16	100
Sub-acute phase: membranous desquamation of fingertips	26	89.7
Perineal desquamation	5	26.3
Irritability	20	69
Gastrointestinal involvement (vomiting, diarrhea, abdominal pain, liver enlargement, jaundice, gallbladder hydrops)	15	48.4
Joint involvement (arthralgias, arthritis)	4	15.4
General status at the time of diagnosis		
Adequate	19	61.3
Fair or poor	12	37.7

* Diagnostic clinical criteria.
SD: standard deviation; IQR: interquartile range.

Treatment

Gammaglobulin was administered to all 31 patients(100%) and, in three cases, medical records did not show whether they had received ASA. Eight patients had fever longer than 24 hours after receiving the first dose of gammaglobulin, therefore, a second dose was administered to 5 of them. In 6 cases, corticosteroids were administered during treatment, two of them had already received a second dose of gammaglobulin. The median time since the onset of symptoms and the administration of gammaglobulin treatment was 7 days (IQR: 7-10) in patients with incomplete KD, a median of 1 day more compared to the complete form of the disease (median: 6; IQR: 5-7.25).

Complications

CAD was detected in 5 patients. It was present in 4 of complete KD cases, and in 1 of incomplete KD. Of the 5 cases, one had two aneurysms with a diameter of 5 mm and 3.4 mm in the left coronary artery and a 6 mm aneurysm in the right coronary artery (risk IV). Another 2 patients had exclusive dilatation of the coronary arteries: one of them, of the right coronary artery of up to 3 mm (Z score: +4.7) and the other patient of the right coronary artery (3 mm; Z score: +3.27) and left coronary artery (2.8 mm; Z score: +2.42), both cases with a grade II risk. The two remaining patients had a grade III risk: in one of them, a dilatation of 2.7 mm of the left coronary artery was seen (Z score: +3.25) together with a 3.6-mm aneurysm in the anterior descending artery. The other child had a 4.7-mm aneurysm in the left main

TABLE 2. *Analytical data*

Laboratory data	Median	Interquartile range
Total leukocytes (cells/mm^3)	15 800	11 400-20 800
Neutrophils (cells/mm^3)	10 200	7900-14 220
Lymphocytes (cells/mm^3)	3800	1700-5313
Platelets (cells/mm^3)	388 000	274 000-514 000
Hemoglobin (g/dL)	11.3	10.4-11.8
Albumin (g/dL)	3.91	3.60-4.05
Bilirubin (mg/dL)	0.37	0.20-0.57
GPT (U/L)	29	16.8-123.3
Sodium (mEq/L)	137	135-138
Potassium (mEq/L)	4.3	4.13-5.05
CRP (mg/dL)	9.73	7.11-16.10
PCT (ng/ml)	2.24	0.18-4.43
ESR after 1 hour (mm)	70	25-102

Analytical data:
GPT (ALT): pyruvate-glutamate transaminase (alanine aminotransferase); CRP: C-reactive protein; PCT: procalcitonin; ESR: erythrocyte sedimentation rate.

coronary artery and coronary ectasia of the left main coronary artery (left anterior descending: 3.3 mm; left circumflex artery: 3.2 mm). In 2 cases, the CAD was on the left side, while in the rest it was bilateral (3/5). Likewise, other heart abnormalities were seen, e.g. pericardial effusion, which was present in 6 patients, of whom one had CAD.

Two patients had complete resolution of their CAD in the ultrasonographic follow-up at 6 weeks. Three patients had coronary changes persistence that did not disappear after one year follow-up.

Risk factors for coronary involvement

The results of the statistical analysis of clinical and analytical parameters studied in patients with and without CAD are shown in *Table 3*. Patients with CAD had a lower albuminemia (3.2 versus 3.99 mg/dL, $p= 0.002$) and had, for a cut-off point <3.5 mg/dL of albuminemia, 100% sensitivity, 92.3% specificity, a positive predictive value (PPV) of 71.4% and a negative predictive value (NPV) of 100%.

Patients with CAD had a higher CRP (median: 16.2 mg/dL versus 8.4 mg/dL, $p= 0.047$) and had, for a cut-off point of CRP >12 mg/dL, 100% sensitivity, 69.2% specificity, a PPV of 38.5% and a NPV of 100%.

The area under the curve (Receiver Operating Characteristic, ROC) for the diagnosis of CAD for CRP (*Figure 1*) and albumin (*Figure 2*) was 0.785 (95% confidence interval [CI]: 0.63-0.94) and 0.938 (95% CI: 0.85-1.00), respectively.

In the subset of patients with complete KD, the presence of gastrointestinal symptoms at the time of admission was related to CAD development ($p= 0.02$), as well as higher bilirubin levels with a median of 0.65 mg/dL (IQR: 0.57-0.98, $p= 0.02$) versus a median of 0.3 mg/dL (IQR: 0.2-0.4) in patients without CAD.

No significant differences were found in the risk of CAD among the complete and incomplete forms of KD at the time of the diagnosis ($p= 1.0$), and a similar coronary injury prevalence was found between both groups (1/7= 14.3% in the incomplete form and 4/24= 16.7% in the complete form).

DISCUSSION

Kawasaki disease etiology is unknown and there are no clinical or pathognomonic laboratory data for its diagnosis, therefore we depend on clinical criteria. However, there are children with incomplete KD that do not meet all criteria but who might have some coronary artery abnormalities. In different studies, the prevalence of the incomplete KD form ranges from 15% to 36.2%[5] of KD cases. The definitions posed by the different authors regarding the incomplete KD form conditions the prevalence of CAD found in the published studies. Sudo et al.[5,8] indicated the presence of CAD in an echocardiography as a mandatory criterion for incomplete KD, so 100% of cases of incomplete KD had CAD. Manlhiot et al.[5,9] defined incomplete KD as fever for ≥5 days and 2 or 3 of the standard criteria, disregarding echocardiographic findings. A similar CAD

TABLE 3. *Results of the statistical analysis in patients with and without coronary artery involvement*

Laboratory clinical data	Without CAD (n= 26) Median (IQR)	With CAD (n= 5) Median (IQR))	*p*-value
Sex*	14/26 male	5/5 male	0.056
No. of days with fever	6.0 (5-7.5)	7.0 (6.5-14)	0.172
Total leukocytes (cells/mm³)	15250 (11375-20125)	19800 (14950-22250)	0.248
Total neutrophils (cells/mm³)	9990 (6818-13700)	14220 (9050-15937)	0.179
Total lymphocytes (cells/mm³)	4200 (2150-5320)	3400 (1168-5620)	0.747
Hemoglobin (g/dL)	11.3 (10.4-12.03)	10.4 (9.8-11.5)	0.170
Platelets (cells/mm³)	411000 (268250-522250)	342000 (233000-576000)	0.707
Albumin (g/dL)	3.99 (3.78-4.10)	3.23 (2.42-3.29)	0.002
Bilirubin (mg/dL)	0.3 (0.2-0.48)	0.63 (0.35-1.31)	0.066
GPT (U/L)	22 (14-123.5)	75 (29-109.5)	0.231
Na (mEq/L)	137 (135-138)	134 (131-138)	0.189
K (mEq/L)	4.3 (4.1-5)	4.2 (3.5-4.7)	0.472
CRP (mg/dL)	8.42 (5.85-15.07)	16.2 (12.17-19.0)	0.047
PCT (ng/mL)	1.73 (0.12-3.52)	4.05 (1.22-)	0.355

* Sex: data are shown in absolute value ratio.
CAD: coronary artery disease; IQR: interquartile range; GPT: pyruvate-glutamate transaminase; Na: sodium; K: potassium; CRP: C-reactive protein; PCT: procalcitonin.

incidence was found in patients with complete KD. In our study, CAD prevalence in incomplete and complete forms was similar (14.3% and 16.7%, *p*= 1.0).

Echocardiography has allowed to detect a considerable number of children with KD and CAD who do not meet the standard criteria.[10]

Given that the presence of CAD is a very restrictive and specific criterion of incomplete KD, the AHA has developed an algorithm with clinical and analytical criteria for the evaluation and treatment of patients in whom incomplete KD is suspected, which we have used as a gold standard in this study. As in other studies,[11] we have found

FIGURE 1. *ROC curve for the diagnosis of coronary involvement based on C-reactive protein*
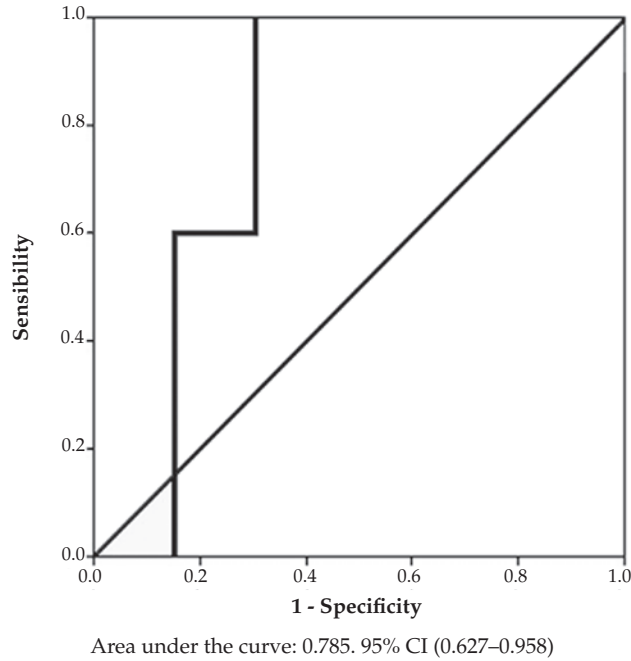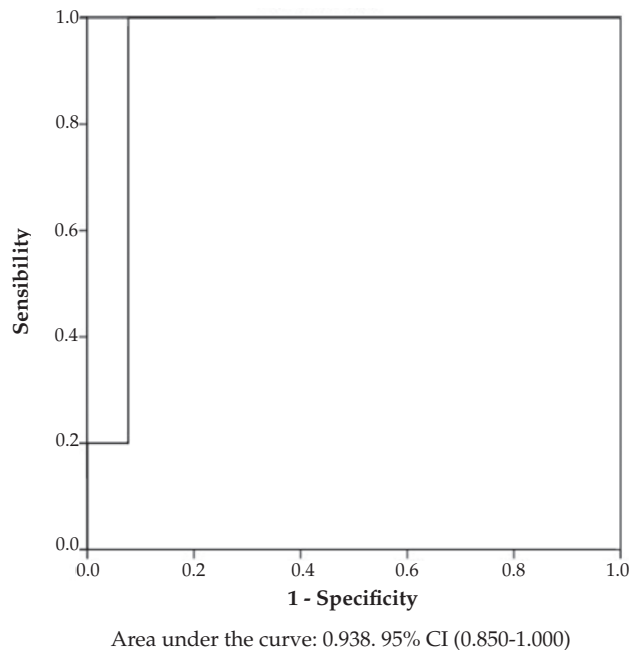

Area under the curve: 0.785. 95% CI (0.627–0.958)

FIGURE 2. *ROC curve for the diagnosis of coronary involvement based on albumin*

Area under the curve: 0.938. 95% CI (0.850-1.000)

a longer diagnostic delay in incomplete forms, which, in our case, has been 24 hours (7 versus 6 days) and that in incomplete forms could be related to a higher risk of developing CAD.

In our series, CRP and albumin levels have been related to the risk of developing CAD, as observed in other studies.[12] In our study, albuminemia has shown an AUC of 0.938, indicating that there is an excellent correlation among the lower albumin values (cut-off point <3.5 mg/dL) and CAD risk. Other previously described risk factors for the development of CAD, like age under 1 year old or older than 9 years old, leukocytosis or hyponatremia were not confirmed in our study, probably because of the sample size limitation. N. Kitano et al,[13] in a cohort of consecutive cases consisting of 1415 patients with KD, found that a rate of patients with CAD was significantly lower in the 11 to 48 month old age group (2%, 17/859), compared to the group of children younger than 11 months old and older than 48 months old (5.2%, 29/556), respectively (*p*= 0.001). These findings agree with our data because 3 out of the 5 patients with CAD were younger than 11 months old and one was older than 48 months old. The other patient was in the intermediate age range (12.1 months old).

Although the presence of gastrointestinal involvement (vomiting, diarrhea, abdominal pain, jaundice, gallbladder hydrops) and higher bilirubin levels in general are not factors related to the risk of CAD. Yi et al[14] studied such possible association and found that gallbladder hydrops and higher bilirubin levels were significantly related. In our study, in the complete form of KD, gastrointestinal symptoms and higher bilirubin levels were also significantly related to CAD. Similarly, K. H. Cho et al.,[15] retrospectively analyzed predictive factors of resistance to immunoglobulin therapy in 311 patients with complete and incomplete KD and found that, in patients with complete KD, total bilirubin levels >0.56 mg/dL were significant predictors of resistance.

In our center, patients with KD are subjected to an echocardiography at the time of the diagnosis and in the course of 6-8 weeks. If they have CAD, they are done serially based on findings. If both are normal, follow-up is discontinued. However, in the study by V. Shah et al,[16] in 92 patients with KD, markers of endothelial damage were examined 8.3 years after having had the disease, and they were compared to the control group. They found that in patients with KD, several of these markers persisted significantly increased both in patients with CAD as well as in those without CAD, which suggested the need of a long term follow-up of all patients who had had KD, even though they did not have CAD.

The main limitation of the study is its retrospective nature, with the inherent biases of this kind of studies. There is not a single definition of "incomplete KD" and this variability might make results differ from one to another study. We have used the definition proposed by the AHA in their worldwide known clinical guidelines. KD is defined by clinical diagnostic criteria, and its diagnosis is conditioned by several factors, e.g. the experience of the doctor taking care of the patient. In this study we tried to include only those patients whose medical records clearly reflected the defined clinical criteria, and the 4 doubtful cases were excluded.

To conclude, the risk of CAD in incomplete KD is similar to that in complete KD. In those patients who meet the defined criteria of incomplete KD, treatment with immunoglobulin should not be delayed so as to avoid a diagnostic delay that would eventually increase CAD risk. In our population, high CRP and low albumin levels and the presence of gastrointestinal involvement and higher bilirubin levels are related to a higher CAD risk. ∎

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