ORIGINAL ARTICLE

Coronary Lesions in Kawasaki Disease

Daño coronario secundario a enfermedad de Kawasaki

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ABSTRACT

Introduction: Kawasaki disease, a vasculitis of unknown origin, is currently the main cause of acquired heart disease during childhood and its main sequels are associated with coronary arteries. Therefore, early identification of possible coronary lesions enables adequate treatment to decrease their occurrence.
Objectives: The aims of this study were to determine the probability of coronary injury in patients with Kawasaki disease, to identify the risk factors for developing coronary lesions and the long-term outcome of these patients.
Methods: A total of 245 children with mean age of 3.48 years were diagnosed with Kawasaki disease between October 1988 and December 2013. Age, sex, clinical and laboratory criteria of Kawasaki disease, echocardiographic findings and long-term outcome were analyzed, and the odds ratio was used to assess their participation as probable risk factors for coronary lesions.
Results: Thirty-nine patients presented coronary lesions: 25 male and 14 female patients with mean age of 2.05 years.
Risk factors were: age < 3 years; prolonged fever ≥ 6 days, erythrocyte sedimentation rate > 50 mm/hr; C-reactive protein > 100 mg/L and hematocrit < 30%. Thirteen patients showed transient coronary artery dilation, 12 solitary small or medium-sized aneurysms, 7 multiple coronary aneurysms, 6 giant coronary aneurysms and one myocardial infarction by severe obstructive lesion. In-hospital mortality was 4‰.
Conclusions: Risk of coronary artery lesions in patients with Kawasaki disease was 15.91%. Risk factors were age under 3 years, fever lasting more than 6 days, erythrocyte sedimentation rate > 50 mm/hr; C-reactive protein > 100 mg/L and hematocrit < 30%. In patients with persistent residual coronary lesions treated conventionally there were no adverse events in the mid- and long-term follow-up.

Key words: Kawasaki Disease - Coronary Aneurysms - Coronary Heart Disease

RESUMEN

Introducción: La enfermedad de Kawasaki, una vasculitis aguda de origen desconocido, es actualmente la principal causa de cardiopatía adquirida durante la infancia y sus principales secuelas están relacionadas con las arterias coronarias, por lo que el reconocimiento temprano de la probabilidad de daño coronario posibilita el tratamiento oportuno para disminuir su ocurrencia.
Objetivos: Determinar la probabilidad de sufrir daño coronario en pacientes con enfermedad de Kawasaki, reconocer los factores de riesgo para el desarrollo de lesión coronaria y la evolución a largo plazo de estos pacientes.
Material y métodos: Se diagnosticó enfermedad de Kawasaki en 245 niños (octubre 1988 - diciembre 2013) con edad media de 3,48 años. Las variables analizadas fueron: edad, sexo, criterios clínicos y de laboratorio de enfermedad de Kawasaki, hallazgos ecocardiográficos y evolución a largo plazo. Se calculó el odds ratio para evaluar las diferentes variables analizadas como probables factores de riesgo de enfermedad coronaria.
Resultados: Presentaron daño coronario 39 pacientes: 25 varones y 14 mujeres; edad media: 2,05 años.
Se identificaron como factores de riesgo la edad < 3 años, la fiebre prolongada ≥ 6 días, la eritrosedimentación > 50 mm/h, la proteína C reactiva > 100 mg/L y el hematocrito < 30%. Trece pacientes mostraron dilatación transitoria de las arterias coronarias, 12 pacientes aneurismas solitarios de tamaño pequeño o mediano, 7 pacientes aneurismas coronarios múltiples, 6 pacientes aneurismas coronarios gigantes y uno infarto agudo de miocardio por lesión obstructiva grave. La mortalidad hospitalaria fue del 4‰.
Conclusiones: La probabilidad de presentar daño coronario en pacientes con enfermedad de Kawasaki fue del 15,91%. Los factores de riesgo para lesión coronaria detectados fueron: edad menor de 3 años, 6 o más días de fiebre, eritrosedimentación > 50 mm/h, proteína C reactiva > 100 mg/L y hematocrito < 30%. En los pacientes con daño coronario residual persistente tratados en forma convencional no hubo eventos adversos durante el seguimiento a mediano y a largo plazos.

Palabras claves: Enfermedad de Kawasaki - Aneurismas coronarios - Cardiopatía isquémica.

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Abbreviations

AMI	Acute myocardial infarction	**LCX**	Circumflex artery
ASA	Acetylsalicylic acid	**ADA**	Anterior descending artery
ESR	Erythrocyte sedimentation rate	**RCA**	Right coronary artery
KD	Kawasaki disease	**PDA**	Posterior descending artery
LCA	Left coronary artery		

INTRODUCTION

Kawasaki disease (KD) is an acute vasculitis of unknown origin. (1) Its most important cardiovascular manifestation is development of coronary aneurysms which may be complicated with thrombosis, ischemic heart disease, early atherosclerosis and sudden death.

It is currently the main cause of acquired heart disease during childhood, (2) reaching 25% in non-treated children. (3) Treatment during the acute phase is directed to control the systemic inflammatory state, avoiding and/or reducing coronary vasculitis to prevent thrombosis, while long-term therapy in patients with coronary lesions is focused in avoiding ischemic heart disease.

The purpose of this work was to assess the possibility of coronary lesions in KD patients in our setting, identify the risk factors for developing coronary aneurysms and assess the long-term outcome of these patients.

METHODS

An observational, longitudinal, analytical study, including 245 children (85 female and 160 male) hospitalized in our institution for acute febrile syndrome and diagnosed with Kawasaki disease, was performed between October 1988 and December 2013. In one case the diagnosis was made at autopsy. Mean age was 3.48 years (range 2-114 months). The diagnosis of KD was performed according to classical clinical criteria: prolonged fever ≥ 5 days plus 4 of the following 5 clinical signs: a) changes in the extremities, b) polymorphous rash, c) bilateral nonexudative conjunctivitis, d) changes in the oral cavity and e) cervical lymphadenopathy. "Atypical or incomplete" forms were included: fever ≥ 5 days plus 2 or 3 clinical criteria and positive acute phase reactants, and children under 6 months with prolonged fever ≥ 7 days with laboratory evidence of systemic inflammation and absence of other confirmed febrile disease. (1, 3)

Patients were evaluated at the beginning of the disease through a complete cardiovascular clinical exam, ECG and color Doppler echocardiogram. The echocardiogram included multiple coronary artery images obtained from different sections to visualize the proximal, medial and distal segments of the left coronary artery (LCA), anterior descending (ADA), circumflex artery (LCX), and right coronary artery (RCA), and the posterior descending artery (PDA). The coronary artery internal diameter, number and site of the aneurysms and presence or absence of obstructive lesions or thrombi were measured. The internal diameter was considered abnormal if it was > 3 mm in children under 5 years of age or > 4 mm in children over 5 years until 2004; subsequently, it was considered abnormal if it had a z score > +2.5. (4, 5)

Coronary ectasia was diagnosed when the coronary artery was dilated but with regular lumen, had increased perivascular echo brightness and absence of the normally decreased distal lumen. Aneurysm was diagnosed when a coronary segment internal diameter was ≥ 1.5 times greater than adjacent segments or it had a patently irregular lumen. (4)

According to the American Heart Association recommendations, aneurysms were considered small when the internal diameter was < 5 mm; medium-sized when the internal diameter was 5 to 8 mm and giant when it was > 8 mm. (6)

Coronary lesions were classified as: grade 1: coronary ectasia; grade 2a: solitary small or medium-sized aneurysm; grade 2b: multiple small or medium-sized aneurysms; grade 3: giant coronary aneurysms and grade 4: coronary stenosis.

The echocardiogram was repeated at 1 or 2 weeks according to the clinical outcome, then at 4-6 weeks and at one year from disease onset in patients without coronary lesion. In patients with single or multiple small or medium-sized aneurysms follow-up was every six months and in children with giant aneurysms every three months during the first year of disease evolution. Thereafter, annual follow-up was done with complete clinical assessment, electrocardiogram and echocardiogram. An annual exercise stress test was added to the evaluation after 5 years of age and a rest/stress myocardial perfusion test (SPECT) after 10 years of age in patients with medium-sized or giant aneurysms, which was repeated every 5 years. A selective coronary angiography was performed in one patient with suspected obstructive coronary lesion and acute myocardial infarction (AMI).

Average follow-up was 13.5 years in patients with coronary lesions.

The variables analyzed as risk factors of coronary lesion were: age, sex, days of fever, clinical diagnostic criteria of typical or atypical KD, and laboratory criteria (complete blood count, platelet count, acute phase reactants, plasma ion concentrations, plasma proteins, liver panel and complete urinalysis).

Statistical analysis

The association between each of the clinical and/or laboratory variables and coronary lesions was analyzed using the chi-square test or Fisher´s exact test for dichotomous variables and Student´s t test or the Mann-Whitney test for continuous variables, according to normal or non-normal distribution. Results were expressed as mean ± standard error of the mean.

The odds ratio and confidence intervals were calculated to evaluate the variables analyzed as probable risk factors to develop coronary disease. A p value < 0.05 was considered as statistically significant.

Ethical considerations:

The protocol was approved by the Institutional Committee. As it was a retrospective analysis of a historical registry, no informed consent was requested from the patients.

RESULTS

The average hospital incidence of KD was 9.8 new cases / year without significant changes during the study period.

Prolonged fever was present in 100% of patients, polymorphous rash in 91%, changes in the oral cavity in 88%, bilateral nonexudative or exudative conjunctivitis in 81%, cervical adenopathy in 75% and changes in the extremities in 39%.

All patients were treated with gamma-globulin and acetylsalicylic acid (ASA) at anti-inflammatory doses until 48-72 hours apyrexia, followed by ASA at antiplatelet doses for at least 6 to 8 weeks in the absence of coronary lesion or during all the period the echocardiogram revealed abnormal coronary artery morphology. Three patients required a second dose of gamma-globulin due to non-clinical response to the initial dose.

Patients were classified into two groups according to echocardiographic evidence of coronary artery abnormalities: Group A without coronary lesions and Group B with coronary lesions.

Group A consisted of 206 patients (135 males and 71 females) with ages ranging from 3 to 114 months (mean: 3.25 years); 134 patients presented a typical form of KD and 72 an atypical or incomplete form.

Group B comprised 39 patients: 25 males (64.1%) and 14 females (35.9%) with mean age of 2.08 years (range 2-102 months). The typical or complete form of KD was diagnosed in 17 patients and the atypical or incomplete form in 22, with no statistically significant difference between them (Tables 1 and 2).

Coronary artery morphological abnormalities were detected in the initial echocardiogram. No late coronary disease cases were diagnosed after gamma-globulin treatment.

Risk factors for coronary lesions in this cohort were: 1) age < 36 months, 2) prolonged fever ≥ 6 days, 3) erythrocyte sedimentation rate (ESR) ≥ 50 mm in the first hour, 4) C-reactive protein > 100 mg/L and 5) hematocrit < 30% (Table 3).

Coronary lesions were classified as:

Grade 1: transient coronary dilation (ectasia) found in 13 patients (33.3%). Coronary ectasia affected the ADA in 8 patients and the ADA and RCA in 5 patients.

Grade 2a: solitary small or medium-sized aneurysm observed in 12 patients (30.77%), located in the RCA in 7 patients and the ADA in 5 patients.

Grade 2b: multiple small or medium-sized aneurysms seen in 7 patients (17.95%), simultaneously affecting the LCA, ADA and RCA.

Grade 3; Giant coronary aneurysms found in 6 patients (15.38%), simultaneously involving the LCA, ADA and proximal, medial and distal portions of the RCA.

Grade 4: coronary stenosis found in one patient (2.56%) with severe ADA and RCA involvement requiring coronary revascularization (Table 4).

In average, coronary lesions were identified on the eighth day of fever. None of the patients had impaired left ventricular function during the acute phase of vasculitis. There was infrequent, mild and transient mitral regurgitation (3%) and no cases of aortic valve regurgitation. Moderate pericardial effusion was detected in 4 patients, associated in all cases to coronary artery giant aneurysms.

Patients with coronary ectasia normalized coronary diameters in the first 45 days of KD. Aneurysms regressed in 100% of patients in the grade 2a group in the first 3 years of follow-up and in 28.6% of grade 2b patients, though without complications during clinical follow-up and exercise stress test and/or myocardial perfusion test. All patients in the 2a and 2b

Table 1. Clinical variables

	N° of patients	Mean age (months)	Sex ratio (M/F)	Typical or complete presentation	Atypical or incomplete presentation	Days of fever
Patients without coronary lesion (Group A)	206	39.24±2.34	1.9/1	134	72	6.9±0.29
Patients with coronary lesion (Group B)	39	25.51±4.91	1.78/1	17	22	9.03±0.55
Statistical significance		p=0.0033	ns	ns	ns	p=0.0002

M: Male. F: Female. ns: not significant

Table 2. Laboratory variables

	Ht (%)	Hb(g/dL)	ESR (mm/h)	CRP(mg/L)	Leukocytosis
Patients without coronary lesion (Group A)	33.58±0.32	11.11±0.14	64.49±3.84	77.84±7.59	13,690±5066
Patients with coronary lesion (Group B)	31.53±0.71	10.21±0.25	84.60±5.61	121.31±13.99	15,036±1505
Statistical significance	p=0.0109	p=0.0057	p=0.0151	p=0.0237	ns

Ht: Hematocrit. Hb: Hemoglobin. ESR: Erythrocyte sedimentation rate. CRP: C-reactive protein. ns: not significant

	OR	95% CI	p
Age < 36 months	4.3175	1.6564-11.2536	p = 0.028
≥ 6 days of fever	24.8000	3.2665-188.3421	p = 0.0019
Erythrocyte sedimentation rate ≥ 50 mm 1st hour	3.7565	1.2777-11.0447	p = 0.0162
C-reactive protein ≥ 100 mg/L	6.0667	1.4266-25.7986	p = 0.0146
Hematocrit ≤ 30%	2.6074	1.0734-6.3335	p = 0.0343

OR: Odds ratio.CI; Confidence interval.

Table 3. Cardiovascular risk factors

	N° of patients	RCA lesion	ADA lesion	LCA lesion
Grade 1	13	5	13	
Grade 2a	12	7	5	
Grade 2b	7	7	7	7
Grade 3	6	6	6	6
Grade 4	1	1	1	

RCA: Right coronary artery. ADA: Anterior descending artery. LCA: Left coronary artery.

Table 4. Coronary lesion in Kawasaki disease

groups received ASA at antiplatelet doses (3-5 mg/kg/day) during aneurysmal coronary dilation.

An infant with grade 2b aneurysms presented with severe peripheral ischemia of the left upper limb leading to gangrene and amputation.

Of the 6 patients with giant aneurysms, 1 died without diagnosis (diagnosed at autopsy) and the other 5 remain asymptomatic, without evident ischemia by non-invasive tests, though with echocardiographic persistence of aneurysmal lesions in all of them. They are currently with permanent anticoagulation therapy and secondary prevention measures of ischemic cardiomyopathy.

A 9-year-old patient with obstructive ADA and RCA admitted to hospital with exercise-induced chest pain, was diagnosed with AMI requiring coronary bypass graft surgery.

DISCUSSION

Kawasaki disease is a childhood acute febrile disease of unknown etiology coursing with disseminated and self-limited vasculitis that predominantly affects young children under 5 years of age. It is an important disease as 15% to 25% of untreated children develop coronary lesions, (1, 3, 7) and is currently the main cause of acquired cardiomyopathy during childhood, surpassing rheumatic fever in Western countries. (2)

The annual incidence of the disease in Hispanic children is 11.1/100,000 children under 5 years of age, (3). In our hospital, which is a regional reference pediatric center, the average incidence was 9.8 new cases / year.

Similar to results reported in the literature, in our series of patients KD occurred mainly in male patients (65.3%) and in those under 5 years of age (67.7%). (7)

The diagnosis of KD is based on clinical criteria established since the original classical description of the disease, with later revisions. (1, 3)

The acute phase of KD may course with pancarditis and mitral and/or aortic valvulitis in addition to the coronary lesion. (3) In our cohort, only 3% of patients had low grade, transient mitral regurgitation that was associated to some degree of coronary lesion in all cases. There were no cases of aortic regurgitation or impaired ventricular function. Moderate pericardial effusion was found in 4/6 patients, all with giant coronary aneurysms, similar to findings reported in the literature. (8)

The main sequels of KD are associated with coronary arteries. Echocardiography is the imaging tool routinely used to evaluate coronary arteries in children, as it detects aneurysms in the proximal portions of coronary arteries with 100% sensitivity and 97% specificity. (3, 9)

During the first period of our study (October 1988-April 2004), 18% of patients with KD presented some type of coronary lesion (10) leading to a local scientific release campaign to disseminate the diagnostic criteria of the disease. In the second period, from April 2004 to December 2013, 12 patients presented coronary lesions over 95 cases diagnosed (12.6%). Although this decrease was not statistically significant, it confirms that the early diagnosis of the disease allows an adequate treatment reducing cardiac consequences.

Risk factors for coronary lesions detected in all the population were: 1) age < 36 months, 2) prolonged fever ≥ 6 days, 3) ESR ≥ 50 mm in the first hour, 4) C-reactive protein > 100 mg/L and 5) hematocrit < 30%.

The disease is more prevalent in males, although this is not a risk factor for coronary lesion, same as the typical or atypical clinical presentation. The rest of the clinical or laboratory components of the disease did not reach statistical significance as risk factors of

coronary lesion in the study population.

Coronary lesions usually appear between the seventh and tenth day of fever, (11) and in our population they were observed after the fifth day, though in average they presented at the eighth day of fever onset. Development of coronary aneurysms is the most severe complication of KD due to its association with myocardial infarction and sudden death.

The most common sites of coronary aneurysms are the proximal ADA and RCA segments, followed by the LCA, LCX, the distal RCA segment and the RCA and PDA junction. (3) In our patients, the proximal RCA and ADA segments were more frequently affected and the distal RCA segment was only involved in patients with multiple giant aneurysms. In this cohort of patients the LCX and/or PDA were not affected.

The disease has an in-hospital mortality of 0.17%, (3) and in our cohort it was 0.4%.

Over time, coronary lesions tend to decrease and disappear, (12, 13) though this process depends on the initial aneurysm size. Regression of small aneurysms occurs frequently, whereas giant aneurysms do not usually regress and tend to progress to stenotic lesions. (13)

In the long-term follow-up, 69.2% of patients with coronary lesions during the acute phase of the disease had a "benign" evolution, particularly all the patients with coronary ectasia or grade 2a aneurysms in which the coronary artery morphologic abnormalities in the echocardiographic image disappeared and myocardial ischemia was not detected by non-invasive methods. Conversely, in 25.7% of patients, coronary abnormalities continued to be evident in the follow-up echocardiogram, and these children continued to be treated with ASA at antiplatelet and/or anticoagulation doses according to the initial aneurysm size. No long-term coronary events were found.

A patient without secondary prevention of ischemic heart disease presented with AMI requiring bypass graft surgery (2.5%) and a baby died undiagnosed and the autopsy revealed severe coronary involvement (2.5%).

The long-term natural evolution of patients with transient coronary dilation is currently unknown, though follow-up for more than 10 years did not show coronary disease or premature atherosclerosis; these patients, however, must undergo periodic controls. (14)

The coronary consequences in patients who have suffered KD may induce premature atherosclerosis causing myocardial ischemia in young adults, especially under 40 years of age, so follow-up and the implementation of secondary prevention measures for ischemic heart disease is essential in these patients. (15)

CONCLUSIONS

The probability of presenting coronary lesions in our KD population was 15.91%. Risk factors detected for coronary lesions were age under 3 years, 6 or more days of fever, ESR > 50 mm/hr, C-reactive protein > 100 mg/L and hematocrit < 30%. Thirty one percent of patients with coronary lesion presented with aneurysmal persistence, acute myocardial infarction or death. Overall mortality was 4‰. In patients with residual coronary lesions treated conventionally for secondary prevention of ischemic heart disease, no adverse events were found at mid- and long-term follow-up.

Conflicts of interest

None declared.
(See author´s conflicts of interest forms in the web / Supplementary Material)

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