Profile of Kawasaki disease in children referred to two pediatric rheumatology services in Rio de Janeiro, Brazil

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ABSTRACT

Objectives: To describe a population of children diagnosed with Kawasaki's disease (KD) in pediatric rheumatology centers of Rio de Janeiro, Brazil, defining the magnitude of the delay period in diagnosing KD and initiating treatment due to confusion with common childhood febrile illnesses and the impact of this delay on the frequency of coronary sequels. **Methods:** Data analysis from hospital records summarized in a dedicated form, including name, gender, age, date of first recorded clinical signs, date of admission to the specialty service, information about symptoms, clinical evolution, intravenous immunoglobulin (IVIG) use and coronary sequels. **Results:** Of 125 patients, 63% were males. 40% were under 2 years at diagnosis. Average lapse between earliest signs and KD diagnosis was 12 days (mean fever duration, 14 d). Only 22.4% had a diagnosis of KD before entering the specialty service. For the remainder, initial hypotheses included: bacterial (60%) and viral infections (12%), rheumatological diseases (4%) and adverse vaccination reactions (1.6%). Hence, prevalent febrile illnesses of childhood were major confounding factors. For records (85.6%) mentioning treatment, 46.7% reported IVIG treatment, beginning after day 10 in 23 cases (21.5%). 20 patients (16%) presented coronary sequels, 9 of which were diagnosed late, including 3 given IVIG after day 10, and 6 given no IVIG. We found no significant association between the frequency of coronary sequels and: a) sex; b) age; c) clinical criteria; d) initiation of IVIG treatment (before or after day 10). **Conclusions:** Common febrile illnesses of childhood often confound the diagnosis of KD.

Keywords: vasculitis, mucocutaneous lymph node syndrome, coronary artery disease, antibiotic prophylaxis.

INTRODUCTION

Kawasaki's disease (KD) is an acute systemic vasculitis of childhood, of unknown cause. The clinical manifestations result from injury to small and medium-sized blood vessels.[1] KD was first described in Japan, where the incidence is highest (140/100.000 in children below 5 year),[2, 3] and further reported worldwide, with variable prevalence. Estimated annual incidence in children below 5 year is 17/100.000 in the USA[4] and 3/100.000 in South America.[5] Clinical and epidemiological patterns suggesting that KD follows exposure to infectious agent(s) include: a) the temporal and geographical distribution; b) a seasonal pattern; c) a low incidence during the first months of life, compatible with passive transfer of immunity from mother to child; d) aggregation of cases, compatible with an infectious outbreak; and e) rarely, a recurrent pattern, compatible with partial resistance to reinfection.[6] From initial reports incriminating human coronaviruses,[7] the list of suspected causative agents[8] has grown to include bacteria, fungi and house mites.

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If left untreated, 15%-25% of children with KD develop coronary sequels, ranging in severity from asymptomatic ectasia of coronary artery to giant coronary aneurisms that lead to thrombosis, myocardial infarction and sudden death.[9-12] Although KD is uncommon, its coronary sequels have a major impact on pediatric care: in industrialized countries, KD is the major cause of acquired heart disease in childhood; in developing countries, it is second only to rheumatic fever.[13-16] The prevalence of coronary aneurisms and overall mortality are effectively reduced by aspirin associated with intravenous immunoglobulin (IVIG). Timing of intervention, however, is reportedly critical to reduce coronary artery disease to 4%-5%.[13-15] According to published studies, improved prognosis requires initiating treatment before the 10th day of fever.[13]

In Brazil, where systematic surveys of KD are insufficient,[17] many infectious diseases, caused by bacterial, viral, protozoan and helminth agents, are considerably more common than KD, but have clinical presentations similar to the initial febrile period of KD, when proper diagnosis and institution of IVIG treatment are believed to be critical. These conditions represent a significant problem for diagnosing KD, especially when there is little awareness of the disease and its sequels.

Here we analysed the clinical evolution of KD in brazilian children, describing the frequency of KD diagnosis, and identifying the alternative hypotheses that were initially considered, as well as the extent to which the diagnosis of KD was delayed by confusion with more common infectious diseases, and the possible impact of these delays on the timing and effectiveness of IVIG therapy.

METHODS

Location and design of the study

We analysed retrospectively the hospital records of KD patients from the pediatric rheumatology services of Instituto de Puericultura e Pediatria Martagão Gesteira (IPPMG) and Hospital Municipal Jesus (HMJE), both from Rio de Janeiro, Brazil, with approval by the Ethics Committee of both institutions. These public tertiary care hospitals provide on-demand specialty care for residents of the state of Rio de Janeiro.

We have included children from 0 to 12 years, admitted from January 1992 to December 2005, who had a diagnosis of KD. Data from the respective records were summarized in a data collection form, including the following entries: name, gender, age, date of first recorded clinical signs, date of admission to the pediatric rheumatology service, information about symptoms, clinical evolution, IVIG use and coronary sequels.

Information related to diagnosis and treatment

The diagnosis of KD and its clinical evolution were established on the basis of the clinical history, date of beginning and cessation of fever, and physical examination. This included the evaluation of extremities, oral cavity, lips, lymph nodes, conjunctivae and rashes. Symptoms related to the gastrointestinal, genito-urinary, cardiovascular, musculoskeletal and respiratory systems, central nervous system, skin and fanera were also investigated. The following complications were detected: hepatitis, uveitis, facial paralysis, neurosensory hypoacusia. With respect to coronary artery injuries, the type of lesion was recorded (ectasia/aneurism). Data were also collected on the recurrence or persistence of fever after initiating treatment, and recurrence of the disease. The type and timing of medication used for treatment of KD were also determined. 14.4% of records did not contain sufficient information about treatment.

Case definition

A case of KD was defined as occurring in a patient who had fever for at least 5 days, in association with at least 4 of the following clinical findings: alterations in the extremities, polymorphic rash, conjunctival hyperemia, typical changes in lips and/or oral mucosa and cervical lymphadenomegaly. Incomplete KD was defined as persistent fever, in association with 2 or 3 of the above findings, in the absence of other diseases which could account for the clinical presentation. Resistant KD was defined by persistent or recurrent fever, 36 h after IVIG infusion. The diagnosis of relapsing KD was made when the criteria for KD were fulfilled in a patient that had already undergone clinical remission. These criteria are detailed in Table 1A.

Statistical analyses

Pearsons Chi-square test with two degrees of freedom was used to evaluated the association between the frequency of coronary sequels and the following variables: a) sex; b) age (under 1 year or above 1 year); c) clinical criteria; d) initiation of IVIG treatment (before or after day 10).

RESULTS

Out of 125 cases (75 from IPPMG and 50 from HMJE) fulfilling criteria for inclusion, prevalence was highest between 2-5 years (37%) (Table 2A). Affected children were predominantly males (Table 2A).

Tablel 1. Criteria for disgnosis of KD adopted in this study

A – Diagnosis criteria for Kawasaki's Disease.

Fever persisting for at least 5 days and at least 4 out the 5 criteria listed below:	
Changes in extremities	Hyperemia and painful edema of hands and feet. Use of the hands and normal walking can become difficult. Perineal desquamation should also be considered.
Polymorphous Rash	Cutaneous eruptions occuring in the first few days, involving the trunk and extremities, and with variable presentations (uticarirform rash, morbilliform maculopapular rash, or diffuse rash reemblilng scarlet fever). No bullae or vesicles are seen.
Conjunctival hyperomia	Bilateral, nonsappurative and painless, with preferential involviment of bulbar conjunctival. There is no corneal ulceration; and can accompany anterior uveitis. It is rarely associated with photophobia.
Changes in lips and oral cavity	Intense hyperemia of lips and oropharynx, fissures, drying of the mucosa and bleeding in the lips. Lingual papillac may become prominent, leading to a characteristic "strawberry" tongue. No ulcerative or exsudative lesions.
Cervical lynphadenomegaly	At least one lymph node with a diameter of 1.5 cm or larger, most commonly unilateral, painful and firm, in the anterior cervical triangle.

B- Most frequent clinical findings

Diagnosis criteria	**N**	**%**
Fever lasting at least 5 days	125	100
Changes in extremities	123	98
Changes in lips and oral cavity	121	96
Rash	103	82
Conjunctival hyperomia	102	82
Lynphadenopathy	84	97

Table 2. Profile of the patients in our study

A

Distribution of patients per sex and age groups at diagnosis	
Sex	37% male; 63% female
Age	%
< 12 months	17
12 a 24 months	23
> 24 months a 5 years	37
> 5 years	23

Only 28 of the 125 patients (22.4%) had a diagnosis of KD before referral to specialty services. Before referral, alternative diagnostic hypotheses were entertained in most cases. These included bacterial infections (60%), viral infections (12%), other rheumatologic diseases (4%) and adverse reactions to vaccination (1.6%).

The duration of febrile illness before treatment initiation, one of the data most relevant to prognosis, was at least 5 days (range from 5 to 38 days, mean 14 days). Fever, in 36% of the patients (n = 45), lasted up to 10 days, and in 3% (n = 8), lasted beyond 30 days. However, the duration of febrile illness was not recorded for 23 patients. On average, diagnosis was made at the 12th day of fever.

Table 1B shows the frequency of different clinical manifestations that are accepted as diagnostic criteria for KD in patients with a fever lasting at least 5 days. All diagnostic criteria were found in a high frequency, and changes in extremities, oral cavity and lips were present in more than 95%. Even with this high frequency of diagnostic criteria, a diagnosis of incomplete KD was made in 7 patients (5.6 %), who had fever associated with 3 of the 5 criteria. In this group, only one case of incomplete KD occurred in a child over 5 years, all other cases being under 2 years.

In Table 2B, we show the frequency of manifestations of previously reported in studies of KD, but which do not qualify as diagnostic criteria by the current consensus. This included gastrointestinal (nausea, vomiting diarrhea, abdominal pain); genitourinary (sterile piuria); musculoskeletal (arthritis, arthralgia, myalgia, claudication); respiratory (cough, tachypnea, pulmonary infiltration, pleural effusion); central nervous (irritability, aseptic menigitis); skin and fanera (alopecia, Beau streaks).

Treatment and therapeutic response

All patients received aspirin, 80-100 mg/kg/day, until they were feverless apyearetic for at least 48 hours. The dose was then reduced to 3-5 mg/kg/day (dose that inhibits platelet aggregation), as a single dose, maintained for 6-8 weeks, except in cases that evolved with coronary artery injuries, in which treatment was continued as recommended. IVIG was administered as a continuous infusion for 10-12 hours at a dose of 2 g/kg to 46%

B

Localization of clinical manifestations with reference to systems involved							
	Gastrointestinal tract	Genitourinary tract	Musculoskeletal system	Respiratory system	CNS	Cardiovascular system	Skin and fanera
%	53	30	46	40	38	16	8
N	66	36	58	50	48	20	10

CNS = central nervous system.

of patients (n = 50) in a total of 107 patient with available treatment records. The timing of infusion with respect to the febrile period is detailed in Table 3A, distinguishing between cases where IVIG was instituted at the recommended period and those in which it was given with delay.

Complications

We found 3 cases of hepatitis, 1 of uveitis, 3 of facial paralysis due to injury of the 7th cranial nerve, and 3 cases of neurosensory hypoacusia. Thrombocytosis occurred in 71% of cases (6 cases had no laboratory test information). Only one child had thrombocytopenia.

All patients had two-dimensional echocardiography at the moment of diagnosis and during the follow-up period. Coronary involvement in the subacute period, manifesting as aneurisms and coronary dilations, was found in a total of 20 patients, only 6 (5% of all cases) of which had been diagnosed and treated before day 10. For 5 additional patients presenting coronary involvement, we have no information about treatment. The remaining 9 patients diagnosed after day 10 included 3 receiving IVIG, and 6 more who could not be treated because of a nationwide shortage of supply. Table 3B shows the distribution of patients presenting coronary sequels as a function of the age group at the time of diagnosis.

No cases of acute myocardial infarction and no fatal outcomes were recorded during the follow-up period. Among patients presenting coronary involvement, 2 presented KD resistant to IVIG infusion, and 1 had incomplete KD.

Impact of different variables on the frequency of coronary sequels

We failed to detect a statistically significant association between the frequency of coronary sequels and any of the following: a) sex (chi-square = 0.05369), not significant/NS) ; b) age (under 1 year or above 1 year) (chi-square = 1.17557), NS); c) clinical criteria (lymphadenomegaly: chi-square = 0.82392, NS; Polymorphous rash: chi-square = 0.57721, NS; Changes in extremities: chi-square = 0.25818, NS; Changes in lips and oral cavity: chi-square = 0.70293, NS; Conjunctival hyperemia: chi-square = 0.01451, NS).

We also examined the effects of IVIG treatment. Treatment had a significant impact (chi-square = 33.65172, $P < 0.001$) on the frequency of coronary sequels. Administration of IVIG starting later than day 10 had no significant effect on the frequency of coronary sequels (chi-square = 2.63017, NS).

Table 3. Use of IVIG and frequency of coronary sequels

A

IVIG treatment			
	%	Time	%
No	45.6		
Yes	40	< 10 days >10 days	54 46
No information Avaiable	14,4		

B

Age with coronary sequels	Number of patientss	%
until 12 months	7	35
1-2 years	4	20
years	9	45
> 5 years	0	0
Total	20	100

IVIG – Intravenous immunoglobulin..

DISCUSSION

KD presents a challenge to the pediatrician working in a tropical country, because it is an uncommon rheumatologic affection that requires highly specific intervention to prevent serious or fatal sequels, but has a nonspecific clinical presentation[18] in the critical period during which proper treatment should be instituted. Many infectious diseases more prevalent than KD, presenting as acute febrile illnesses of childhood, may confound the diagnosis of KD.

KD was first described in Japan in 1961,[19] and further characterized in 1974[9] from the clinical, epidemiological and anatomopathological standpoints.[20] Our data agreed with previous studies concerning the predominance of affected males and the age of diagnosis (under 5 years in 77% of cases).[6,15] Incomplete KD is more common before 2 years old, and the affected children seem to be at greater risk of developing coronary disease.[21] In our study, 6 of the 7 patients with incomplete KD were less than 2 years old, and 1 of these evolved with coronary lesions. Resistant KD, described in 10% to 15% of subjects, is associated to a greater risk of ectasias or aneurisms.[22-24] This clinical evolution was observed in 7 of our patients (5%), with heart involvement in 2 of these cases (1.6%). Recurrent KD, which has been reported in 3%-5% of Japanese children,[6] was observed in 2 of our subjects (1.6 %).

In our study, most delays in diagnosis were due to difficulties in distinguishing KD from bacterial and viral infections and adverse reactions to vaccines, which together constituted the initial diagnostic hypotheses in ~75% of cases. Hence, the

impact of prevalent febrile illnesses of childhood on the timing of diagnosis and treatment of KD is considerable. Because these represent a problem common to many tropical countries, our findings should raise awareness in pediatricians elsewhere.

The diagnosis of KD relies on the observation of nonspecific signs and symptoms, such as high fever persisting for at least five days, in association with four out of five diagnostic criteria, which can be observed in the first few weeks of evolution.[15] Most frequent findings are: changes in the oral cavity, conjunctival hyperemia, exantema, changes in extremities and cervical lymphadenopathy.[12,25] These findings may be overlooked by parents or caretakers, or attributed to fever, and further go unreported, as they are often taken for irrelevant or obvious. Overall, the lack of an alarming initial presentation likely delays the search for medical care.

The mean time of duration of fever (14 days) in our study shows a marked delay in diagnosis, contrasting with 6.5 days in a canadian study.[26] Importantly, KD can be diagnosed by the 4th day of fever, on the basis of 4 or more diagnostic criteria.[15]

Among the patients with properly information about treatment, only 54% of cases that used IGIV, received it in the recommended period. We could not find in our study a significant effect of initiating treatment after the recommended period.

In conclusion, delayed diagnosis of KD in Brazilian children led to initiating IVIG treatment after the recommended period in a considerable number of patients of our study, but this delay had no significant impact in the frequency of coronary sequels.

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