Kawasaki Disease in the Older Child

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ABSTRACT. *Objectives.* To determine the prevalence of Kawasaki disease in older children and to evaluate its clinical presentation, time to diagnosis, and outcome in comparison with younger patients with the disease.

Methodology. A retrospective analysis of all patients discharged with a diagnosis of Kawasaki disease at a pediatric tertiary care hospital over a 12-year period.

Results. A total of 133 patients were included in this study; 7.5% were 9 years of age or older at the time of illness. Patients were grouped by age: infants included children age 1 to 8 years of age and children 9 years of age or older. Older children had a higher frequency of abnormal cardiovascular physical examination (50%) versus children (6%) and infants (10%). The older age group and the infants had a higher prevalence of coronary artery abnormalities and poor left ventricular function than did the 1- to 8-year-olds. Eighty percent of the older children had coronary arteries that were either dilated or aneurysmal, and 30% demonstrated left ventricular dysfunction on initial echocardiography. The number of days to diagnosis after meeting the diagnostic criteria was 5.8 ± 2.3 for infants, 5.2 ± 1.5 for older children, and 1.9 ± 0.3 for children. Older children had a complicated course of Kawasaki disease compared with younger patients.

Conclusion. We found a higher prevalence of older children with Kawasaki disease at our center than has previously been reported. Older patients, as well as infants, had a higher rate of coronary artery abnormalities than did the children between 1 and 8 years of age. Older age at the time of illness or a delay in treatment may be important factors in determining cardiac involvement in Kawasaki disease. *Pediatrics* 1998;102(1). URL: http://www.pediatrics.org/cgi/content/full/102/1/e7; *Kawasaki disease, coronary arteries, intravenous immunoglobulin.*

ABBREVIATIONS. KD, Kawasaki disease; CVS, cardiovascular; ECG, electrocardiography; LV, left ventricular; WBC, white blood cells; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; ASA, acetylsalicylic acid.

Since its first description in the Japanese literature in 1967,[1] much has been written about Kawasaki disease (KD). A systemic vasculitis, KD is characterized by fever, mucocutaneous manifestations, and musculoskeletal changes, and its most devastating effects are on the heart, particularly the coronary arteries. The etiology of KD remains unknown, and its presentation can be diverse.[2,3] The illness usually affects infants and children younger than 3 years.[1] KD is extremely uncommon in patients 9 years of age and older.[4–6] The most recent epidemiologic survey from Japan found that <1% of cases occurred in children 9 years of age and older.[6]

Our experience suggested that KD affecting older children was more common than reported previously. Our clinical impression was that most of the older patients were diagnosed late in the course of their illness and, consequently, had more morbidity associated with the illness. Of interest to us were reports suggesting that cardiac sequelae are more common in patients younger than 6 months and 9 years of age and older.[6,7] As a result of the paradox between the existing medical literature and our clinical impressions, we conducted this study to determine the prevalence of KD in older children and to evaluate its clinical presentation, time to diagnosis, and outcome in comparison with younger patients with the disease.

METHODS

Our hospital is a tertiary care facility in a large urban center and serves as the referral center for the province of British Columbia (population, 3.7 million) for pediatric cardiology, rheumatology, and intensive care. The charts of all inpatients diagnosed with KD from January 1, 1984, to September 30, 1996, inclusive, were reviewed. This study period coincided with our current medical record database. The list was compared with our own cardiology database for completeness. The following variables were recorded: age at onset, duration of hospitalization, duration of fever, treatment modality, cardiac investigations, and complications. The dates of the onset of illness, fulfillment of diagnostic criteria, diagnosis, and treatment all were noted. We also examined the time interval in days after which the diagnostic criteria were met until the diagnosis was made.

An abnormal cardiovascular (CVS) examination was defined as the presence of signs of congestive heart failure, ie, systemic or pulmonary venous congestion, gallop rhythm, or cardiomegaly. The incidental finding of congenital heart disease was considered separately. Electrocardiography (ECG) findings were considered abnormal if there was ST segment elevation, T-wave changes, Q waves, or conduction disturbances. ECG was performed with an ATL (Bothell, Washington) or a Vingmed (Horten, Norway) ultrasound machine. Echocardiograms were considered abnormal if there was any abnormality of the coronary arteries or if there was abnormal left ventricular (LV) function. The coronary arteries were imaged using standard parasternal short axis views, following the coronaries in the atrioventricular groove with the four-chamber view, as has been described previously.[8,9] Coronary artery abnormalities were defined as echogenic if the lumen was clearly irregular or if there was mural prominence with normal dimensions; dilated if the intraluminal diameter was ≥3 mm in

children 5 years of age and younger and ≥4 mm in children older than 5 years; and aneurysmal (including giant aneurysms) if the intraluminal diameter was ≥4 mm in children younger than 5 years of age and ≥5 mm in children older than 5 years.[9–12] In this study, we did not differentiate between different morphologies of aneurysms (ie, fusiform, saccular). LV function was assessed qualitatively by wall motion as well as by M-mode, using a shortening fraction of <28% as abnormal.

The patients were placed into one of three groups: group A included those 1 year or younger at the time of illness; group B included 1- to 8-year-olds; and group C included those 9 years of age and older. There have been reports describing the atypical nature of KD in infants[2,13] and, therefore, this group was considered separately. Because several large series have few patients older than 9 years of age,[6,14,15] this was chosen as the lower age limit for the older group.

The mean and SEM or the median and range were calculated for all of the descriptive variables. Nominal data were analyzed using χ^2 analysis or the Fisher's exact test. Initial analysis was completed using 3×2 contingency tables. If the overall association was statistically significant, 2×2 contingency tables were used to determine more specific associations. A general linear models analysis of variance was used to determine whether differences existed in the continuous data among the three groups of patients. If statistical differences were found, a Student–Newmann–Keuls multiple range test was used to determine which groups differed.

Because multiple comparisons were made, P values <.005 were considered statistically significant; values between .005 and .05 were considered to indicate associations that were of marginal statistical significance and worth additional consideration, and values >.05 were considered statistically insignificant. All of the statistical analyses were completed using SAS Statistical Software (SAS Institute Inc, Cary, NC).

RESULTS

From January 1, 1984, to September 30, 1996, a total of 133 children with KD were discharged from British Columbia's Children's Hospital. Seventeen patients who were admitted for investigation of possible KD in whom the diagnosis was not made were excluded from the review. The age and gender data for the three groups are shown in Table 1. Ten patients were 9 years or older at time of illness (group C). This represents 7.5% of our study population. All of these patients fulfilled the diagnostic criteria. As seen in Table 1, 6 patients from groups A and B did not fulfill the diagnostic criteria; however, the diagnosis was made on the basis of echocardiographic findings in 4 patients and clinical suspicion in the remaining 2 patients. These patients were not included in the time-to-diagnosis analysis (see below). Table 2 compares the clinical characteristics examined; there were no differences in the duration of fever, but the older patients were more likely to have an abnormal CVS examination compared with the younger patients ($P < .001$).

The diagnosis of KD was made before the diagnostic criteria were met in 19 patients, of whom 17 were in group B and 2 in group A. The diagnosis was made within 48 hours of meeting the diagnostic criteria in 6 patients in group A, 43 patients in group B, and 1 patient in group C. Therefore, the diagnosis of KD was made promptly in 38.1% of group A patients, 58.8% of group B patients, and 30% of group C patients, respectively. The mean interval from the diagnostic criteria being met until diagnosis of KD was made was significantly longer in infants and older children ($P < .003$) (Table 2).

Additional laboratory investigations are summarized in Table 3. Although the white blood cell (WBC) and platelet counts were higher in infants ($P < .0001$ and $P < .0001$, respectively), the erythrocyte sedimentation rate (ESR) was higher in the older patients ($P < .04$). There was no difference in the prevalence of abnormal ECG findings among the three groups of patients.

There was a higher prevalence of abnormal initial echocardiograms in children 9 years and older. They had more echocardiographic abnormalities of the coronary arteries than did children between 1 and 8 years of age, with 80% having coronary arteries that were either dilated or aneurysmal. As well, 30% of the older children demonstrated abnormal LV function on initial echocardiography (Table 4). Recognizing that many physicians consider 7-year-olds with KD atypical, we also analyzed our data with the 7- and 8-year-old patients in group C. With the inclusion of these patients, group C still had a higher prevalence of abnormal CVS examinations and echocardiograms and took longer to defervesce than did the group of patients 1 to 6 years of age ($P < .003$, $P < .006$, and $P < .04$, respectively). However, there was no difference in the time to diagnosis between the two groups.

Several patients had a complicated course that included congestive heart failure, intensive care admission for inotropic support and ventilation, or readmission for recrudescence of symptoms. This included 24% of group A patients, 13% of group B patients, and 50% of group C patients (group C > group B; $P < .002$). One infant (0.8%) died from a myocardial infarction 1 month after his initial hospitalization for KD. Autopsy findings showed occlusion of the coronary arteries as a result of intimal proliferation.

At our center, treatment was initiated at the time of

TABLE 1. Number of Patients, Age, Gender, and Number of Diagnostic Criteria Met

		Group A Age ≤1 y	Group B 1 < Age < 9 y	Group C Age ≥9 y
Number of patients		21	102	10
Age (mo)*		6.8 ± 0.5	43.3 ± 2.1	130.8 ± 5.5
Male:female ratio		0.9:1	2.2:1	1:1
Diagnostic criteria	3	1		
	4	2	3	
	5	11	15	2
	6	7	84	8
	Total	21	102	10

* The mean ($\bar{x}$) ± SEM are reported.

TABLE 2. Fever, Initial CVS Findings, Delay in Diagnosis, and Length of Hospital Stay*

	Group A Age ≤1 y	Group B 1 < Age < 9 y	Group C Age ≥9 y
Fever (days)	11.5 ± 1.1	10.1 ± 0.5	12.7 ± 0.9
Cardiovascular findings			
Normal	19	96	5
Abnormal	2	6	5†
Days to diagnosis after criteria met	5.8 ± 2.3	1.9 ± 0.3‡	5.2 ± 1.5
Length of hospital stay (days)	13.5 ± 6.2	5.7 ± 0.5	8.2 ± 1.4

The mean (x̄) ± SEM are reported.
† Group C had a significantly higher proportion of abnormal CVS findings than did either group A or group B (*P* < .001).
‡ The time to diagnosis is significantly shorter in group B than in either group A or group C (*P* < .003).

TABLE 3. Laboratory Investigations*

	Group A Age ≤1 y	Group B 1 < Age < 9 y	Group C Age ≥9 y
Peak WBC count	24.1 ± 2.1†	15.8 ± 0.7	14.4 ± 2.5
Peak platelets	843.8 ± 73.1‡	535.2 ± 25.8	521.1 ± 77.5
ESR	71.8 ± 5.7	81.6 ± 3.7	107.6 ± 10.6§
ECG (*n* = 124)			
Normal	14	85	6
Abnormal	6	9	4
Initial ECG (*n* = 132)			
Normal	11	74	1
Abnormal	10	27	9‖

* The mean (x̄) ± SEM are reported.
† Group A had a significantly higher peak WBC count than did either group B or group C (*P* < .0001).
‡ Group A had a significantly higher peak platelet count than did either group B or group C (*P* < .0001).
§ Group C had a significantly higher ESR than did either group A or group B (*P* < .04).
‖ Group C had a higher proportion of abnormal ECG findings than did either group A or group B (*P* < .001).

TABLE 4. Findings on Initial and Follow-up ECG

	Group A Age ≤1 y	Group B 1 < Age < 9 y	Group C Age ≥9 y
Normal coronaries	11	74	1
Abnormal coronaries	10*	27	9†
Echogenic	2	9	1
Dilated	6	11	6
Aneurysmal	2	7	2
2-Year follow-up			
Normal	9	24	6
Abnormal	1‡	3	3
LV function			
Normal	20	97	7
Abnormal	1	4	3§

* The proportion of patients with abnormal coronary arteries in group A is higher than in group B (*P* < .001).
† The proportion of patients with abnormal coronary arteries in group C is higher than in group B (*P* < .03).
‡ The patient with abnormal coronary arteries died.
§ The proportion of patients with LV function is higher in group C than in group A or group B (*P* < .004). One patient did not undergo ECG (group B).

diagnosis (Table 5). In the era before treatment with intravenous immunoglobulin (IVIG) was standard at this center (1986), patients were treated with acetylsalicylic acid (ASA). One patient in group B did not receive ASA with their IVIG. No comparison was made between the original regimen of IVIG to the current standard (400 mg/kg/day for 4 days vs 2 g/kg/day once). Patients who failed to defervesce within 48 hours of treatment with IVIG or ASA were more likely to have coronary artery abnormalities on initial echocardiography (*P* < .006). Among this group of patients, 12/26 in group B and 5/5 in group C had abnormal coronary arteries. Among those pa-

tients who received a second course of IVIG for ongoing symptoms, 3/6 in group B and 2/2 in group C had abnormal coronary arteries.

DISCUSSION

The diagnosis of KD can be challenging because the criteria may be present only fleetingly and may be missed. Our study confirmed the atypical nature of KD in infants.[2,13] There was a greater time interval from meeting the diagnostic criteria to making the diagnosis, and a higher proportion of coronary artery abnormalities in infants compared with children 1 to 8 years of age. However, the coronary abnormalities resolved on follow-up. Young age has been cited as a favorable factor in the resolution of coronary aneurysms.[12] The one death in our study population was of an infant. This is comparable with mortality reported previously.[16]

The diagnosis of KD may be missed in the older child with fever of unknown origin. We have diagnosed KD in an 11-year-old patient who fulfilled the diagnostic criteria for 2 months. Recently, we cared for a 15-year-old patient in whom the diagnosis of KD was suspected, but not made. Six months later, she presented with angina attributable to myocardial infarction. Angiography showed diffuse coronary artery disease, and she has since undergone coronary artery bypass grafting.

The older group was not identifiably different from the other two groups and, apart from their age, they did not have atypical presentations (Table 1). However, they had more cardiac involvement, and there was a trend toward a longer time to defervesce after treatment was initiated. Only one patient in the

TABLE 5. Treatment and Time to Defervescence

	Group A Age ≤1 y	Group B 1 < Age < 9 y	Group C Age ≥9 y
IVIG + ASA	18	83	9
ASA only	3	18	1
IVIG only		1	
Second dose IVIG	1	6	2
Corticosteroids		2	1
Defervescence in 48 hours*			
IVIG/ASA	Yes = 13; no = 2	Yes = 52; no = 26	Yes = 4; no = 5
ASA only	Yes = 2; no = 1	Yes = 12; no = 7	

* Patients who were afebrile at the time of treatment (n = 31) were excluded from the analysis of time to defervescence.

older age group had normal coronary arteries on initial echocardiography. The time interval to make the diagnosis for patients 9 years and older was greater than twice that for patients 1 to 8 years old. All but one patient in the older age group had their illness in the latter 5 years of the study; thus, the delay in diagnosis is not likely to be attributable to a lack of awareness of KD. This suggests that KD was considered an unlikely origin of the fever in the older children.

It has been suggested that treatment with IVIG is most efficacious when administered early in the course of the illness.[17,18] However, we still administer IVIG to patients who are diagnosed with KD, regardless of the duration of their illness. Longer duration of fever before treatment has been associated with coronary aneurysm formation.[3] In our study, patients who failed to defervesce within 48 hours after treatment with IVIG or ASA were more likely to have coronary artery abnormalities and LV dysfunction than those who defervesced. In addition, 55% of patients who received a second course of IVIG for ongoing symptoms had abnormal coronary arteries.

Two of the three older patients who were diagnosed promptly and treated went on to have a complicated course. Both developed congestive heart failure, were admitted to the intensive care unit, and did not defervesce with IVIG treatment. They went on to develop coronary artery abnormalities. Delay in diagnosis and treatment in the older patients, therefore, was not the only risk factor for a poor clinical course in KD.

The majority of coronary artery abnormalities resolve within 2 years of the illness.[5,19] In our study, almost all of the echocardiographic abnormalities normalized within 2 years, except in the older age group, in which there was a trend toward more residua on follow-up. However, new evidence suggests that KD may result in long-term damage to the coronary microcirculation, even in the apparent absence of coronary involvement during the acute phase of the illness.[15,20]

A study of this type has some limitations. The prevalence of older patients (9 years and older) in our study, compared with other series, may naturally reflect some selection bias. Because we are the tertiary center for the province, we do see a greater proportion of complicated cases of KD, and the nature of KD in the older patients suggests that they would be referred to our hospital. Even those patients not managed here during the acute phase of the illness would have been referred for outpatient follow-up, because we are the only center in the province that performs pediatric echocardiography. Another potential limitation of our study is that not all patients had angiography to definitively diagnose coronary artery abnormalities.[21]

CONCLUSION

We found a substantially higher prevalence of older patients with KD at our hospital than has been reported previously in the medical literature. The older patients, as well as the infants, had a higher rate of coronary abnormalities than children 1 to 8 years of age. A study of this type cannot determine whether the delay in diagnosis and, therefore, a delay in treatment were responsible for the higher rate of complications. However, KD in the older child, as well as in the infant, may represent a variant of the disease in terms of its severity. Pediatricians must include KD in the differential diagnosis of fever without a focus in the older child.

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