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REVIEW ARTICLE

Sequelae of Kawasaki Disease in Adolescents and Young Adults

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Kawasaki disease is an acute vasculitis of unknown etiology that predominantly affects children <5 years of age. Structural damage to the coronary arteries after the acute, self-limited illness is detected by echocardiography in ~25% of untreated patients. The long-term effects of the acute coronary arteritis are unknown. To define the spectrum of clinical disease in young adults that can be attributed to Kawasaki disease in childhood, we performed a retrospective survey of cases reported in the English and Japanese published data of adult coronary artery disease attributed to antecedent Kawasaki disease. The mean age at presentation with cardiac sequelae was 24.7 ± 8.4 years (range 12 to 39) for the 74 patients identified with presumed late sequelae of Kawasaki disease. Symptoms at the time of presentation with cardiac sequelae included chest pain/myocardial infarction (60.8%), arrhythmia (10.8%) and sudden death (16.2%). These symptoms were precipitated by exercise in 82% of patients. One-third of the patients in whom a chest radiograph was taken had ring calcification. Angiographic findings included coronary artery aneurysm (93.2%) and coronary artery occlusion (66.1%). Extensive development of collateral vessels was reported in 44.1% of patients. Autopsy findings included coronary artery aneurysms (100%) and coronary artery occlusion (72.2%). The acute vasculitis of Kawasaki disease can result in coronary artery damage and rheologic changes predisposing to thrombus formation or progressive atherosclerotic changes that may remain clinically silent for many years. Coronary artery aneurysms and calcification on chest radiography were unusual features in this group of patients. A history of antecedent Kawasaki disease should be sought in all young adults who present with acute myocardial infarction or sudden death.

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Damage to the coronary arteries as a sequela of Kawasaki disease was first recognized by Kato et al. in 1975 (1). Angiographic and echocardiographic studies have documented coronary artery aneurysms in ~25% of untreated patients (2,3). Studies of the natural history of these lesions suggest that they may remodel as a result of myointimal proliferation, or they may persist and develop stenosis of the vessel lumen at the outlet of the aneurysm (3). Postmortem studies have demonstrated that the inflammatory insult to the endothelium and coronary artery wall creates a focus for subsequent accelerated atherosclerosis (4). Treatment with high doses of intravenous gamma globulin and aspirin during the first 10 days of fever reduces the prevalence of coronary artery abnormalities detected by echocardiography (2). Unfortunately, many cases of Kawasaki disease are misdiagnosed as other childhood illnesses associated with rash and fever, and appropriate therapy is not administered. Coronary artery lesions may develop in these children and remain silent until adulthood (Fig. 1).

To characterize the late cardiac sequelae of this vasculitis, we reviewed the clinical, angiographic and pathologic data from reports of young adults presenting with coronary artery disease attributed to antecedent Kawasaki disease. We restricted our search to cases reported after 1967 in the Japanese published data and after 1974 in the English reports. These dates correspond to the first reports by Dr. Kawasaki in Japanese and English, respectively (5,6). To focus on the late sequelae of Kawasaki disease and to avoid confusion with other forms of adult coronary artery disease, only patients aged 12 to 40 years at the time of presentation with cardiac sequelae were included.

Review of the Data

We identified a total of 74 patients, 40 from the English reports (7–40) and 34 from the Japanese data (41–73). The demographic data for both groups are presented in Table 1. There were 57 males (77%). The male preponderance is consistent with the reported male/female ratio of 1.5:1 for children with the acute Kawasaki disease (74). The mean age at presentation with cardiac sequelae was 24.7 ± 8.4 years (range 12 to 39). Of the 62 patients for whom ethnicity was specified, 53 (85.5%) were of Asian extraction.

The symptoms and clinical findings at the time of presen-

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Figure 1. A 43-year old white man who was a conditioned athlete presented with abrupt onset of symptoms of myocardial infarction after 30 min of strenuous cycling. An angiogram of the left coronary artery showed aneurysmal dilation of the left main, left anterior descending and left circumflex arteries. A thrombus occluded the left anterior descending artery (**arrowhead**). The distal segments were normal, with a smooth vessel lumen and no evidence of atherosclerosis. The patient had no risk factors for cardiovascular disease. The patient's mother reported a history of a "scarlet fever-like illness" at age 5 years (1958) associated with prolonged fever (>1 week), high fevers, nonpruritic rash and photophobia.

tation with cardiac sequelae are summarized in Table 2. More than half of the patients presented with chest pain due to myocardial infarction. Ten patients (13.5%) presented with symptoms related to decreased cardiac output or arrhythmia. Six patients (8.1%) were asymptomatic and were identified during investigation of an abnormal screening electrocardiogram or chest radiograph. Twelve patients (16.2%) died suddenly; their cardiovascular disease was discovered at autopsy.

A description of the patients' activity at the time of symptom onset was specified for 39 patients. A high percentage (82%) were engaged in vigorous exercise.

A chest radiograph was abnormal in 21 (63.6%) of 33 patients. A striking radiographic finding of ring calcification representing calcium deposition in the walls of the coronary artery aneurysms was noted in ~36% of patients. The majority of patients had abnormalities of the electrocardiogram, echocardiogram and exercise test, suggesting decreased coronary artery blood flow.

Table 1. Demographic Features of 74 Patients

Age at presentation with cardiac sequelae (yr)	24.7 ± 8.4
Range	12–39
Male gender	57 (77%)
Ethnicity identified	62 (83.8%)
Japanese	50 (80.6%)
Korean	1 (1.6%)
Chinese	1 (1.6%)
Asian (unspecified)	1 (1.6%)
Black	4 (6.4%)
White	5 (8.1%)

Data presented are mean value ± SD or number (%) of patients.

Table 2. Symptoms and Clinical Findings

Symptoms at Presentation	No. (%) of Patients (n = 74)
Chest pain/myocardial infarction	45 (60.8%)
Arrhythmia	8 (10.8%)
Fatigue/dyspnea	2 (2.7%)
Sudden death	12 (16.2%)
Abdominal pain	1 (1.3%)
No symptoms/abnormal ECG or CXR	6 (8.1%)
Event associated with exercise	32 (82%)
Clinical findings: CXR abnormal	21/33 (63.6%)*
Cardiomegaly	8 (24.2%)
Ring calcification	12 (36.4%)
ECG abnormal	47/53 (88.7%)*
Exercise test abnormal	9/17 (52.9%)*

*Number of patients with abnormality/number of patients studied. CXR = chest radiograph; ECG = electrocardiogram.

The angiographic findings in surviving patients are summarized in Table 3. Aneurysms of the coronary artery were present in more than 90% of patients. Aneurysms were located in all three major segments of the left coronary artery. The right coronary artery was frequently involved (62%). Complete occlusion of a coronary artery segment was observed in 39 (66.1%) of 59 patients. Prominent collateral vessels were specifically described in approximately one-half of the patients.

The medical and surgical interventions in surviving patients are described in Table 4. More than 50% of the patients were treated with bypass surgery. All grafts remained patent, although the range of patient follow-up varied between 0.4 and 9 years. Fifteen patients were treated conservatively with either medication or observation. Two of these patients died—one while awaiting bypass surgery and one 6 months after initiation of medical therapy.

Table 3. Angiographic Findings

	No. (%) of Patients (n = 59)
Coronary aneurysms	55 (93.2%)
Location of aneurysm	
LMCA	21/50 (42%)*
LAD	19/50 (38%)*
LCx	14/50 (28%)*
RCA	31/50 (62%)*
Occlusion of coronary artery	39 (66.1%)
Location of occlusion	
LAD	21 (53.8%)
LCx	5 (12.8%)
RCA	24 (61.5%)
Prominent collateral vessels	26 (44.1%)

*Number of patients with finding number of patients with location specified. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

Table 4. Medical and Surgical Interventions in Surviving Patients

Intervention	No. (%) of Patients (n = 44)
Angioplasty	5 (11.4%)
Surgical intervention	
Coronary artery bypass surgery	26 (59.1%)
Iliac bypass surgery	1 (2.3%)
Hepatic artery aneurysm resection	1 (2.3%)
Medical intervention	
Anticoagulation	9 (20.4%)
Medical treatment*	3 (6.8%)
No intervention	3 (6.8%)

*Digitalis, diuretic drugs or calcium channel blocking agents, alone or in combination.

Eighteen patients died with cardiovascular complications attributed to antecedent Kawasaki disease (Table 5). Thirteen (72.2%) of the 18 patients died during strenuous physical exercise. Aneurysms of at least one coronary artery were noted during the postmortem examination in all 18 patients. Calcification of the aneurysms was reported in 12 patients. In 10 (55.5%) of 18 patients, the distal coronary arteries were specifically described and no atherosclerotic changes were found.

Cardiovascular risk factors for the study group were tabulated (Table 6). For the 45 patients in whom risk factors were specifically mentioned, one-half had no cardiovascular risk factor other than antecedent Kawasaki disease. These data suggest that the inflammatory insult during Kawasaki disease is sufficient to cause clinically significant coronary artery disease in adulthood in the absence of other risk factors.

Data were collected describing the childhood illness presumed to be Kawasaki disease. In 44 patients, the year of presentation of the childhood illness could be determined. Cases apparently occurred as far back as the 1950s, predating Dr. Kawasaki's first report by over a decade. A description of the antecedent illness presumed to be Kawasaki disease was provided for 39 patients (52.7%). Twenty-five patients had fever longer than 5 days, 15 (38.5%) of 39 patients met 4 of the 5 clinical criteria and 7 (17.9%) of 39 patients met 3 of the 5 criteria. No antecedent illness could be recalled by 18 (24.3%) of the 74 patients.

Table 5. Autopsy Findings in Patients Who Died of Cardiovascular Complications After Presumed Kawasaki Disease

	No. (%) of Pts With Aneurysm (n = 18)	No. (%) of Pts With Obstruction (n = 13)	Total No. (%) of Pts
Vessel diseased			
LMCA	10 (55.6%)	3 (23.1%)	
LAD	11 (61.1%)	6 (46.1%)	
LCx	2 (11.1%)	2 (15.4%)	
RCA	13 (72.2%)	8 (61.5%)	
LCA	0 (0%)	2 (15.4%)	
Calcification of aneurysms			12/18 (66.7%)*
Absence of atherosclerosis in nonaneurysmal segments			10/18 (55.5%)*
Evidence of previous infarction			7/17 (41.1%)*

*Number of patients (Pts) with finding/number of patients with finding specified. Other abbreviations as in Table 3.

Table 6. Cardiovascular Risk Factors

	No. (%) of Patients (n = 45)
No risk factors identified	22 (48.9%)*
Diabetes	1 (2.2%)
Hypertension	4 (8.9%)
Hypercholesterolemia	2 (4.4%)
Family history of heart disease	2 (4.4%)
Tobacco use	6 (13.3%)

*Number of patients with data available.

The diagnosis of Kawasaki disease was established during childhood in 11 patients. None were thought to have suffered coronary artery damage as a result of Kawasaki disease and therefore were not monitored for late complications of their disease. In one patient, the echocardiograms taken at the time of acute illness (age 3 years) were described as normal. This patient suffered a myocardial infarction 9 years later.

Discussion

We reviewed the records of 74 patients reported in the English and Japanese reports who presented with cardiovascular disease attributed to Kawasaki disease in childhood. The coronary artery abnormalities in these patients included coronary artery aneurysms with calcification, stenosis, obstruction and extensive collateral vessels. The spectrum of clinical complications included myocardial infarction, arrhythmia, heart failure and sudden death. The case report of a 42-year old male with focal aneurysmal dilation of the left coronary artery and acute myocardial infarction illustrates several of the common features in this group of patients. First, the patient had no risk factors for coronary artery disease, and angiography demonstrated isolated left coronary artery dilation with smooth arterial walls and no evidence of atherosclerosis. Myocardial infarction occurred during strenuous exercise in this patient and in 82% of the reviewed cases. Although conclusive documentation of antecedent Kawasaki disease was lacking, a prolonged illness with fever and rash at age 5 years (9 years before Dr. Kawasaki's first publication) was reported by the mother.

The possible contribution of antecedent Kawasaki disease to the genesis of cardiovascular disease in adults was investigated by Kato et al. in Japan (75). A survey of 354 hospitals identified 130 adult patients with coronary artery aneurysms; 21 patients had a definite (2 cases) or suspected history (19 cases) of Kawasaki disease in childhood. The investigators suspected that many of the remaining 109 patients might have

had antecedent Kawasaki disease, but information regarding childhood illness was not available. Because Kawasaki disease primarily affects children <5 years of age, patients are usually unable, as adults, to recall details of their childhood illness. Many cases of Kawasaki disease are misdiagnosed during the acute illness because the disease shares many features with other childhood illnesses, such as scarlet fever and measles. The workers stressed the importance of parental interviews to obtain a history of antecedent Kawasaki disease.

Patients with aneurysms caused by Kawasaki disease had a strikingly high prevalence of left main coronary artery disease (42%), as compared with patients with atherosclerotic coronary aneurysms reported in the National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS) (4%) (76). The right coronary artery was a frequent site of aneurysms in both groups (Kawasaki disease 62%; CASS 69%). Another unusual feature of the patients with antecedent Kawasaki disease was ring calcification on the chest radiograph, which was noted in 36.4% of patients in whom a chest radiograph was obtained.

The majority of patients underwent coronary artery bypass graft surgery as treatment for their obstructive coronary artery disease. These young, otherwise healthy patients may be particularly suitable candidates for bypass surgery because their aneurysms are usually localized to the proximal vessel segments and the distal segments are free of disease.

In summary, Kawasaki disease in childhood can cause permanent coronary artery damage that may remain clinically silent until adulthood. A history of a Kawasaki-like illness in childhood should be sought for patients presenting with coronary artery aneurysms in the absence of generalized atherosclerotic disease.

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