Grown-up Kawasaki disease patients who have giant coronary aneurysms

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Background: **Many Kawasaki disease (KD) patients have reached adulthood in Japan. The current status of adult patients who have giant coronary aneurysms with KD is not well understood.**

Methods: **Medical records of 48 KD patients (33 males and 15 females) with giant coronary aneurysms (maximum coronary artery internal diameter >8 mm) aged 20 years or over were retrospectively reviewed.**

Results: **The age of the patients at the diagnosis of KD ranged from 0.3 to 12.8 years (median 2.9 years) and the age of the patients in this review ranged from 20.0 to 33.1 years (median 25.2 years). During the follow-up period, the maximum coronary artery internal diameter ranged from 8.2 to 30.0 mm (median 10 mm). Giant coronary aneurysms progressed to coronary artery stenosis and/or complete occlusion in 34 (74%) of 46 patients. Coronary artery bypass graft surgery was performed in 9 (19%) of 48 patients. Myocardial infarction occurred in 14 (31%) of 45 patients. Other complications or problems occurred in 5 patients with angina pectoris, low left ventricular ejection fraction, ventricular tachycardia, hemorrhagic cerebral infarction, or thyroid carcinoma respectively. In the patients followed up, 4 dropped out. In addition, 1 patient succeeded in pregnancy and delivered a baby.**

Conclusions: **Close attention should be paid to ventricular tachycardia in adult KD patients with giant coronary aneurysms, especially for those who have low left ventricular ejection fraction. To reduce the number of dropped out patients, it is important that the patients should be referred to a new doctor when they change their place of residence.**

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Introduction

About 40 years have passed since the first report of Kawasaki disease (KD),[1] and a great number of KD patients have subsequently grown to adulthood. In 2003, the guidelines for the diagnosis and management of cardiovascular sequelae in KD were published.[2] However, a proper diagnostic procedure or treatment for KD patients with giant coronary aneurysms (maximum coronary artery internal diameter >8 mm) who have grown to adulthood has not yet been established. According to the nationwide database of the Japanese Kawasaki disease registry in 2006, 90 000 KD patients are now more than 20 years old.[3] Even after the introduction of high-dose intravenous gamma globulin (IVGG), 0.35% of KD patients were diagnosed as having giant coronary aneurysms.[4] KD patients with coronary artery aneurysms may have long-term coronary risk factors, and atherosclerotic lesions might develop in adulthood.[5] However, the present situation of KD patients with giant coronary aneurysms is not well understood. To follow up adult KD patients with giant coronary aneurysms, it is important to know the patients' condition. The present study was conducted using a questionnaire survey about the present situation of grown-up KD patients with giant coronary aneurysms.

Methods

This study retrospectively reviewed the multi-center medical records of 48 KD patients (33 males and 15 females) with giant coronary aneurysms aged 20 years and over by December 31, 2005 who were diagnosed with KD based on the criteria revised (2nd edition) in 1974, 1978 (3rd edition), or 1984 (4th edition) by the Kawasaki Disease Committee of Japan.[6]

The questionnaire was sent to 62 institutions by mail. The contents of the questionnaire included: 1) the age at diagnosis of KD; 2) the maximum coronary artery internal diameter measured by 2-dimensional echocardiography or coronary artery angiography (CAG) during follow-up; 3) the initial treatments in the acute phase of KD; 4) the age at the first and the final CAG; 5) the location of giant coronary aneurysms; 6)

the outcome of giant coronary aneurysms (progression to coronary artery stenosis or complete occlusion); 7) the history of coronary artery bypass graft surgery; 8) the present medical institution, the specialty of physicians, the frequency of visits, current medication, and the contents of medical examinations; 9) cardiac symptoms and complications; 10) social activity (employment, attending university, or pregnancy); and 11) smoking habits. This investigation was conducted with full respect to the privacy of patients, and information without identification data was collected from medical records.

Giant coronary aneurysms were defined with a maximum coronary artery internal diameter >8 mm shown by 2-dimensional echocardiography or CAG. Coronary artery stenosis was defined with a coronary artery internal diameter of 50% or less than that of the adjacent coronary artery by CAG. Seventeen institutions responded and 62 patients were included. In 14 patients excluded, 2 died before adulthood and 12 did not have giant coronary aneurysms (maximum coronary artery internal diameter ≤8 mm). Statistical analysis was made using the Chi-square test and Fisher's exact test. $P<0.05$ was considered statistically significant.

Results

Altogether 48 KD patients with giant coronary aneurysms were analyzed. The age of the patients at the diagnosis of KD ranged from 0.3 to 12.8 years (median 2.9 years), and their age in this review ranged from 20.0 to 33.1 years (median 25.2 years). There were 3 KD patients with giant coronary aneurysms who had two episodes of the acute phase of KD. During the follow-up period, the maximum coronary artery internal diameter, measured by 2-dimensional echocardiography or coronary angiography ranged from 8.2 to 30.0 mm (median 10 mm). As to the initial treatment in the acute phase of KD, 38 patients were treated with oral aspirin, 3 patients were treated with flurbiprofen and dipyridamole (n=2) or flurbiprofen alone (n=1), and 2 patients were treated with dipyridamole or ticlopidine hydrochloride. Two patients were treated without medication and there were no oral medication records in 3 patients. Gamma globulin therapy and corticosteroid therapy were used in 11 and 5 patients, respectively (Table 1).

All the patients had CAG, and the first CAG was performed at 0.1 to 10.8 years (median 0.3 years) after the diagnosis of KD; the age of the patients for the first CAG was 0.6 to 15.1 years (median 3.9 years). The final CAG was performed at 2.2 to 23.2 years (median 12.8 years) after diagnosis; the age of the final CAG was 6.6 to 25.5 years (median 17.0 years). The locations of giant coronary aneurysms identified by CAG are shown in Table 2. Follow-up CAG revealed that 14 patients had coronary artery stenosis, 14 patients had complete occlusion, and 6 patients had both coronary artery stenosis and complete occlusion. Twelve patients had neither coronary artery stenosis nor complete occlusion. There were no medical records of CAG in 2 patients. Nine KD patients with giant coronary aneurysms underwent coronary artery bypass graft surgery (Table 2).

The present situations of the KD patients with giant coronary aneurysms are shown in Table 3. The patients were followed up at different institutions by pediatricians or adult cardiac physicians. The reasons for the drop-outs were: moving out of the original registration district (2 patients), attending university (1), and lack of consciousness-of-disease (1). The frequency of hospital visit varied for the patients.

The current medication for the patients is shown in Table 3. Thirteen patients including the 4 dropped-out patients had no medication records. In their adulthood, CAG was performed in 7 of the 22 patients by pediatricians and in 2 of the 20 patients by adult cardiac physicians. The frequency of CAG decreased after transfer to adult cardiac physicians; however, no significant difference in the frequency of CAG was observed between pediatricians and adult cardiac physicians (the Chi-square test and Fisher's exact test). CT and/or MRI was done in 4 of 22 patients by

Table 1. Clinical features and the initial treatment in the acute phase of Kawasaki disease (KD)

Gender	Male/Female = 33/15
Age at the diagnosis of KD (y)	0.3–12.8 (median 2.9)
Age at this review (y)	20.0–33.1 (median 25.2)
Maximum coronary artery internal diameter (mm)	8.2–30.0 (median 10)
Initial treatment in the acute phase of KD	n=48
Aspirin therapy	38
Aspirin alone	20/38
Aspirin with antiplatelets or anticoagulants	18/38
Other NSAIDs	3
Flurbiprofen with dipyridamole	2/3
Flurbiprofen alone	1/3
Other antiplatelets	2
Dipyridamole alone	1/2
Ticlopidine hydrochloride alone	1/2
Without medication	2
No record	3
Gammaglobulin therapy	n=48
None	30
Treated	11
No record	7
Corticosteroid therapy	n=48
None	36
Treated	5
No record	7

NSAIDs: non-steroidal anti-inflammatory drugs.

Table 2. CAG and coronary artery bypass graft surgery

First CAG	Years after the diagnosis of KD (y)	0.1–10.8 (median 0.3)
	Age at that time (y)	0.6–15.1 (median 3.9)
Final CAG	Years after the diagnosis of KD (y)	2.2–23.2 (median 12.8)
	Age at that time (y)	6.6–25.5 (median 17.0)
Locations of giant coronary aneurysms		*n*=48
	LAD	14
	LCX	1
	RCA	12
	LAD and LCX	4
	LAD and RCA	16
	LAD, LCX and RCA	1
In the follow-up CAG		*n*=48
	Coronary artery stenosis	14
	Complete occlusion	14
	Both coronary artery stenosis and complete occlusion	6
	Neither coronary artery stenosis nor complete occlusion	12
	No record	2
Coronary artery bypass graft surgery		*n*=9
	Years after the diagnosis of KD (y)	2.7–21.3 (median 10.6)
	Age at surgery (y)	3.4–25.0 (median 12.6)

CAG: coronary artery angiography; LAD: left anterior descending coronary artery; LCX: left circumflex artery; RCA: right coronary artery.

Table 3. Present situation in Kawasaki disease patients with giant coronary aneurysms

Institutions		*n*=48
	Medical university hospitals	21
	General hospitals	19
	Children's medical center	2
	Private medical clinics	1
	No record	1
	Dropped out	4
Specialty of physician		*n*=44
	Pediatricians	22
	Adult cardiac physicians	20
	No record	2
The frequency of visit		*n*=44
	Every month	8
	Every other month	3
	One time per 3 months	19
	One time per 6 months	3
	One time per year	3
	One time per two years	2
	No record	6
Current medication		*n*=44
	Aspirin alone	17
	Aspirin, warfarin, and other antiplatelets	9
	Aspirin and warfarin	4
	Aspirin and other antiplatelets	5
	No record	9
CAG after reaching adulthood		
	Pediatricians	7/22
	Adult cardiac physicians	2/20
CT/MRI after reaching adulthood		
	Pediatricians	4/22
	Adult cardiac physicians	6/20

pediatricians and in 6 of the 20 patients by adult cardiac physicians. CT and/or MRI was done increasingly after transfer to adult cardiac physicians; however, no significant difference in the frequency of CT and/or MRI was observed between pediatricians and adult cardiac physicians (the Chi-square test and Fisher's exact test). ^{201}Tl myocardial scintigraphy and/or exercise stress test was performed in 3 patients who had coronary artery stenosis, in 6 patients who had complete occlusion, and in 6 patients who had neither coronary artery stenosis nor complete occlusion. Neither ^{201}Tl myocardial scintigraphy nor exercise stress test was given to the patients who had both coronary artery stenosis and complete occlusion (*n*=6).

Cardiac symptoms, complications, social activity, pregnancy, and smoking habits are shown in Table 4. Cardiac symptoms such as chest pain or palpitations appeared in 6 patients. Myocardial infarction occurred in 14 (41%) out of the 34 patients who had coronary artery stenosis and/or complete occlusion, in 2 out of the 14 patients who had coronary artery stenosis, in 8 out of the 14 patients who had complete occlusion, and in 4 out of the 6 patients who had both coronary

Table 4. Cardiac symptoms, complications, social activity, and habits

Cardiac symptoms		*n*=48
	None	37
	Chest pain	5
	Palpitation	1
	No record	1
	Dropped out	4
Complications		*n*=48
	Myocardial infarction	14
	None	31
	No record	3
	Other complications or problems	5
	Angina pectoris	1
	Low left ventricular ejection fraction	1
	Ventricular tachycardia	1
	Hemorrhagic cerebral infarction	1
	Thyroid carcinoma	1
Social activity		*n*=48
	Working	24
	Attending university	11
	Housewife	1
	Require home care	1
	No record	7
	Dropped out	4
Pregnancy and delivery (of 15 females)		1/15
Currently pregnant (of 15 females)		1/15
Smoking habits		*n*=48
	None	28
	Smoking	2
	No record	14
	Dropped out	4

artery stenosis and complete occlusion. No myocardial infarction developed in the remaining 14 patients who had neither coronary artery stenosis nor complete occlusion. Other complications or problems occurred in 5 patients. Physical activity was restricted in 9 patients. As to the social activities, 24 patients were working for different bussiness, 11 were attending universities, 1 became a housewife, 1 had a hemorrhagic cerebral infarction under home care, and 7 had no medical records. With regard to pregnancy and delivery in 15 female patients, 1 patient succeeded in pregnancy and delivered twice without any complications and 1 patient was pregnant at the time of investigation. For risk factors of atherosclerosis, current smoking status was recorded in 2 male patients.

Discussion

This study demonstrated that 34 patients (74%) had coronary artery stenosis and/or complete occlusion, and 9 (19%) of 48 patients underwent coronary artery bypass graft surgery. Twelve patients (25%) had neither coronary artery stenosis nor complete occlusion. The long-term results of KD patients with giant coronary aneurysms reported by Kato et al[5] were that 46% of giant coronary aneurysms progressed to coronary artery stenosis or complete occlusion. In this study, the frequency of coronary artery stenosis or complete occlusion was higher than that found by Kato et al (P=0.037, the Chi-square test). The higher incidence of coronary artery stenosis or complete occlusion may be resulted from the longer follow-up in this study. The follow-up period in this study was 10-31 years but that of Kato et al was 10-21 years.

In this study, the treatment of acute phase KD varied. Although aspirin was prescribed in 38 of the 48 patients, flurbiprofen, dipyridamole, ticlopidine hydrochloride, or warfarin was also used. Moreover, 11 patients were treated with IVGG, and 5 patients were treated with corticosteroids. The diagnosis of KD began from 1974 until 1995 and the treatment of acute phase KD was not available after the first description of KD in Japan. Hence, the treatment of acute phase KD varied in this study. Currently, acute phase KD is treated with aspirin and high-dose IVGG,[7,8] and the incidence of coronary artery aneurysms has decreased from 25% to 1.8%.[4,5]

In our study, aspirin alone was prescribed in 17 patients (39%), and aspirin and warfarin combined with other antiplatelets in 9 patients (20%), aspirin and warfarin in 4 patients (9%), aspirin and other antiplatelets in 5 patients (11%). Thirteen patients including dropped-out patients (n=4) had no medication records. It was reported that aspirin and warfarin in combination with high-dose IVGG in acute phase KD are recommended for patients with giant coronary aneurysms, and aspirin and warfarin produce a lower incidence of coronary artery stenosis or coronary artery occlusion in chronic phase KD.[9]

In adulthood, CAG was performed in 7 of the 22 patients by pediatricians and in 2 of the 20 patients by adult cardiac physicians in this study. The frequency of CAG decreased in the patients who were treated by adult cardiac physicians compared with those treated by pediatricians. The usefulness of MRI and multi-slice spiral CT for the visualization of the coronary artery was reported previously,[10,11] and the visualization of the coronary artery by MRI or multi-slice spiral CT has become increasingly popular in adult KD patients in recent years.[3] Therefore, the frequency of CAG in adult patients with giant coronary aneurysms may decrease in the future.

In our study, ventricular tachycardia was observed in 1 patient and low left ventricular ejection fraction in another patient. As reported, two adult patients with a presumed history of KD required implantable defibrillators because of ventricular tachycardia and low left ventricular ejection fraction.[12] Hence, in adult KD patients with low left ventricular ejection fraction, monitoring is particularly necessary. But we should also pay attention to ventricular tachycardia in adult KD patients with giant coronary aneurysms.

In our study, one patient became pregnant and delivered babies twice, and another patient became pregnant but did not deliver during the period of the study. The most important problem in pregnancy and delivery of KD patients with coronary artery lesions was thrombosis of the coronary artery.[13] In a previous study, 7 KD patients with giant coronary aneurysms or complete occlusion who were treated with aspirin or without medication during pregnancy and delivery had no episodes of thrombosis of the coronary artery.[13] Another report presented a KD patient with coronary aneurysm who was successfully treated with heparin during pregnancy and delivery.[14] Also pregnancy and delivery were successful in a KD patient with a giant coronary aneurysm after coronary artery bypass graft surgery.[15] Various treatments were given during pregnancy and delivery in KD patients with coronary artery lesions. There are guidelines available for pregnancy and delivery in KD patients at present. Therefore, standard treatments during pregnancy and delivery in KD patients are mandatory.

Smoking habits were recorded in 2 male KD patients with giant coronary aneurysms in the present study. Smoking, obesity, and hypercholesterolemia are known risk factors for atherosclerosis. Coronary aneurysms constitute a risk factor for atherosclerosis using pathological research in adolescents and young

adults.[16] Thus the prevention of lifestyle-related diseases is required, particularly in those with giant coronary aneurysms. Prohibition of smoking and prevention of obesity should be emphasized by pediatricians before introduction to adult cardiac physicians.

Four of our patients (8.3%) stopped visiting doctors because of moving out of their initial area of registration, attending university, or lack of consciousness-of-disease. The previously reported drop-out rate for patients was 8.6% for patients with persistent coronary aneurysms over 10-21 years of follow up.[5] To reduce the number of dropped-out patients, patients should be referred to a new doctor when they change their place of residence.

The present study has certain limitations. The questionnaire was sent to 62 medical institutions, but only 17 institutions responded, mainly medical university hospitals and general hospitals. Therefore, there may be some bias.

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