

Long-term prognosis of Kawasaki disease patients with coronary artery obstruction

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Summary. The prognosis of coronary artery obstruction was studied in patients with Kawasaki disease. Between May 1973 and December 1987, coronary artery obstruction was diagnosed by coronary angiography in 30 patients (21 males, 9 females), of whom, only 8 (26.7%) had clinical symptoms. One patient died after 9 years of illness. Two complained of frequent chest pain, which disappeared after bypass surgery in one case and spontaneously in the other. Five had symptomatic myocardial infarction. Myocardial ischemia was diagnosed in 31.8% by treadmill stress testing, but was well demonstrated in 85.7% by thallium-201 myocardial tomography. Frequent ventricular premature beats, Wenckebach-type atrioventricular block, and ST-segment depression accompanied by chest pain were recognized by 24-h Holter monitoring. In the past, the methods used to determine the prognosis of Kawasaki disease patients with coronary artery obstruction were not adequate. However, the examinations used in this study revealed an improved ability to determine the prognosis in this disease. Myocardial tomography, in particular, provided a more accurate evaluation of myocardial damage. Ventricular arrhythmias seem to be a serious problem in these patients. Therefore, careful observation using these tests, especially myocardial tomography and Holter monitoring, should be done even if the patients are free of symptoms.

Key words: Kawasaki disease – Coronary artery obstruction – Treadmill stress test – Thallium-201 myocardial tomography – Long-term prognosis.

It has become evident that patients with giant coronary aneurysm in Kawasaki disease should be carefully evaluated because of the poor prognosis [1]. We have previously reported that coronary artery obstruction occurred in 30% of patients with such a giant aneurysm [2]. At present, there is no way to prevent giant aneurysm formation completely, although therapy for Kawasaki disease using high-dose gamma-globulin may reduce aneurysm formation to some extent. Until some preventive measure is found, some of the patients with this complication will continue to show progression to coronary artery obstruction. In this study, we investigated the long-term prognosis of coronary artery obstruction in Kawasaki disease.

Patients and methods

During a 15-year period from May 1973 through December 1987, coronary angiography was performed 572 times on 454 patients with Kawasaki disease. Thirty patients (21 males, 9 females, aged 5–21 (mean 11.5) years) were diagnosed as having total coronary artery obstruction (Table 1). The numbers of patients with obstruction in the coronary arteries were 4 in the left main trunk (LMT), 8 in the left anterior descending (LAD), 2 in the left circumflex (LCX), and 20 in the right coronary artery (RCA). Four patients with RCA obstruction had obstruction of another vessel, 3 with LAD, and 1 with LCX. One patient died after 9 years of illness and two patients discontinued follow-up observations. With the exception of these three, all patients have been followed up until the present (2–17 years of observation, mean 13.1 years). Of these 30 patients, 10 underwent bypass surgery.

Clinical features that occurred after acute illness were reviewed. In addition to routine examinations, including standard 12-lead electrocardiography, chest X-ray, and two-dimensional echocardiography, we evaluated these patients by exercise stress electrocardiography, 24-h Holter electrocardiographic recording and myocardial imaging.

The electrocardiogram during treadmill exercise according to the Bruce protocol was evaluated in 22 patients over the age of 5 years. A test result was considered to be abnormal if the J

Table 1. Patients with coronary obstruction

Case	Age	Sex	Obstruction	Other involvements
1	11 ^a	F	LMT	A, S (RCA)
2	17	M	LAD	A, TT (RCA)
3	20	M	RCA	A (LCA)
4	18	F	RCA	
5	21	M	LMT	
6	20	M	RCA	A (LCA)
7	19	M	RCA	A (LCA)
8	16	F	LCX, RCA	A (LMT, LAD)
9	14	F	LAD	S (LMT, RCA)
10	12	M	LCX	
11	14	M	RCA	
12	13	M	RCA	S (LAD)
13	17	M	RCA	
14	11	F	LAD	
15	9	M	LAD, RCA	
16	12	M	RCA	A (LAD)
17	9	M	RCA	A (LAD)
18	8	F	LMT	A (RCA)
19	8	M	LAD	A (LMT)
20	9	M	RCA	A, S (LCA)
21	6	M	LAD, RCA	
22	7	M	LAD, RCA	A (LCX)
23	5	M	LMT	
24	7	M	RCA	A (LCA)
25	7	M	RCA	A (LCA)
26	7	F	RCA	A (LCA)
27	7	M	RCA	
28	7	M	LAD	A (LCA, RCA)
29	6	F	RCA	
30	9	F	RCA	A (LCA)

^a Patient died at 11 years of age.

LCA, left coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; LMT, left main trunk artery; A, aneurysm; S, stenosis; TT, abnormal tortuosity of the coronary artery

junction was depressed at least 1 mm below the control level and was accompanied by a flattening of the ST segment.

Cardiac tomography using thallium-201 during coronary vasodilation induced by intravenous administration of dipyridamolc (0.7 mg/kg for 4 min) was evaluated in 21 patients.

Fifteen patients underwent 24-h Holter electrocardiographic recording. Two exploring electrodes were attached at V1 and V5, and 2 negative electrodes were attached to the left shoulder and suprasternum: the ground electrode was attached to the right shoulder. The purpose of adding the V5 location was to have a lead for the detection of ischemic ST depression. The patients performed usual activities at school or at home and continued all sports except swimming.

Results

Only 8 patients (26.7%) had clinical symptoms (Table 2). One patient (case 1) suddenly lost consciousness after 6 years of illness. Coronary angiography revealed complete obstruction of the LMT and an aneurysm with stenosis in the RCA. Immediately after the angiography, an aorta-coronary bypass operation was performed. The patient was free

Table 2. Clinical symptoms in patients with coronary obstruction

Case	Obstruction	Clinical symptom
1	LMT	consciousness loss, sudden death
2	LAD	symptomatic myocardial infarction
5	LMT	symptomatic myocardial infarction
9	LAD	symptomatic myocardial infarction
18	LMT	chest pain
19	LAD	symptomatic myocardial infarction
23	LMT	symptomatic myocardial infarction, chest pain

LMT, left main trunk artery; LAD, left anterior descending artery

of symptoms until 3 years after the operation, when she suddenly died while exercising at school. The autopsy demonstrated that the LMT was totally obstructed early in its course. The saphenous vein graft was thickened and the lumen narrowed, but there were no fresh thrombi in any arteries. Two patients had complained of frequent chest pain, which disappeared after an aorto-coronary bypass operation in one case (case 18) and spontaneously in the other (case 23). Of the 30 patients with obstruction, five experienced symptomatic myocardial infarction. All but one were not given antiplatelet drugs, but these patients had been acutely ill before 1976, when knowledge of thrombotic coronary artery obstruction in Kawasaki disease was extremely limited.

In 7 patients (31.8%), the result of treadmill stress testing (Table 3) was positive. Among the positive patients, 4 had obstruction of the LMT and 3 had obstruction of the LAD. Only one (case 18) of the positive patients complained of chest pain during the exercise. In this patient, who had obstruction of the LMT, exercise ST depression was found to have disappeared following surgical treatment. In all patients with ischemic findings, ST depression appeared as the heart rate increased. There were no patients in whom ST depression continued after cessation of exercise. In addition to these 7 patients with an ischemic ST segment response, one patient (case 11) showed increased premature ventricular beats during exercise.

Of 21 patients who underwent thallium-201 myocardial tomography (Table 3), 18 (85.7%) showed abnormal findings. Three patients in whom ischemic ST depression was demonstrated by treadmill stress test, also had abnormal findings in this test. The remaining four with positive findings in the treadmill stress test were former patients and, thus, were not examined by myocardial tomography. Thirteen patients with negative findings in the treadmill stress test were newly found to have ischemia by myocardial tomography. Two patients had persistent perfu-

Table 3. Treadmill performance and results of thallium-201 myocardial tomography in patients with coronary obstruction

Case	Obstruction	Results of treadmill test	Results of myocardial imaging
1	LMT	Positive	
2	LAD	Positive	
3	RCA	Negative	TD (RCA)
5	LMT	Positive	
6	RCA	Negative	TD (RCA)
8	LCX, RCA	Negative	N
9	LAD	Positive	
10	LCX	Negative	N
11	RCA	Negative*	TD, PD (RCA)
13	RCA	Negative	TD (RCA)
14	LAD	Negative	TD (LAD)
15	LAD, RCA	Negative	TD (LAD)
16	RCA	Negative	TD (RCA)
17	RCA	Negative	TD (RCA)
18	LMT	Positive	TD (LMT)
19	LAD	Negative	PD (LAD)
20	RCA		TD (RCA)
21	LAD, RCA		TD (LAD)
22	LAD, RCA	Negative	TD (LAD, RCA)
23	LMT	Positive	TD (LMT)
24	RCA	Negative	TD (RCA)
25	RCA	Negative	TD, PD (RCA)
26	RCA	Negative	N
27	RCA	Negative	PD (RCA)
28	LAD	Positive	TD (LAD)

Positive, ischemic ST segment depression present; Negative, ischemic ST segment depression absent; TD, transient perfusion defect; PD, persistent perfusion defect; N, negative; parentheses: location of abnormal findings; LMT, left main trunk artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery

*Case 11 showed increased premature ventricular beats during exercise without ischemic ST segment response.

Table 4. Results of 24-h Holter monitoring (ECG)

Case	Obstruction	Result of Holter ECG
11	RCA	frequent PVB
14	LAD	A-V block (Wenckebach type)
18	LMT	depression of ST

PVB, premature ventricular beat; A-V block, atrio-ventricular block; LMT, left main trunk artery; RCA, right coronary artery; LAD, left anterior descending artery

sion defects in the territory of the obstructed coronary artery. Two had transient perfusion defects accompanied by a persistent defect in part, and 14 had transient perfusion defects. Only three patients (cases 8, 10, 26) had normal findings using this procedure. Negative cases included two with LCX obstruction and one with RCA obstruction. In case 18, abnormal findings were improved by bypass surgery.

Results of 24-h Holter monitoring (Table 4) showed ST segment depression accompanied by

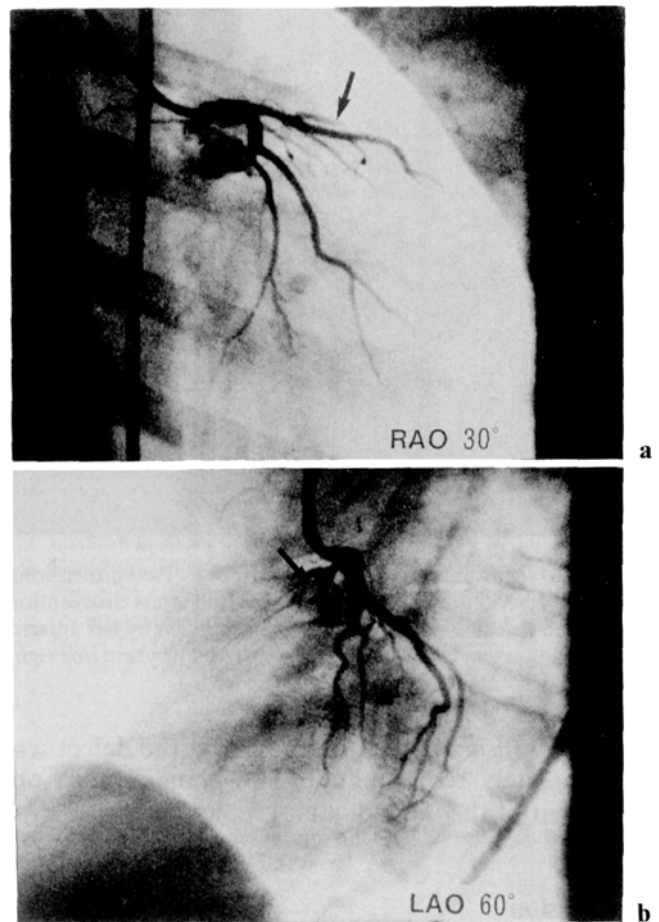


Fig. 1a,b. Angiograms of the left coronary artery showing **a** right anterior oblique 30°, **b** left anterior oblique 60°, and obstruction of the left anterior descending artery (arrow)

chest pain occurred in case 18. Frequent premature ventricular beats occurred in case 11. The number of premature beats within 24-h was 1300, and they were unifocal. Wenckebach-type atrioventricular block occurred in case 14, and this was seen only during sleep.

Case report

Case 14 was a 12-year-old girl. She had Kawasaki disease when she was 6 months old. The first angiography, performed 3 months after onset, demonstrated a giant aneurysm in the left coronary artery. Follow-up angiographies performed 5 and 10 years after the initial examination demonstrated total obstruction of the LAD (Fig. 1). The patient underwent the treadmill stress test after the third coronary angiography. No ST depression was observed during or after exercise. We stopped this test at stage V because of leg fatigue, but the maximal heart rate reached 200 beats/min. Figure 2 illustrates the result of thallium-201 myocardial tomography performed after the third angiography. Anterior perfusion de-

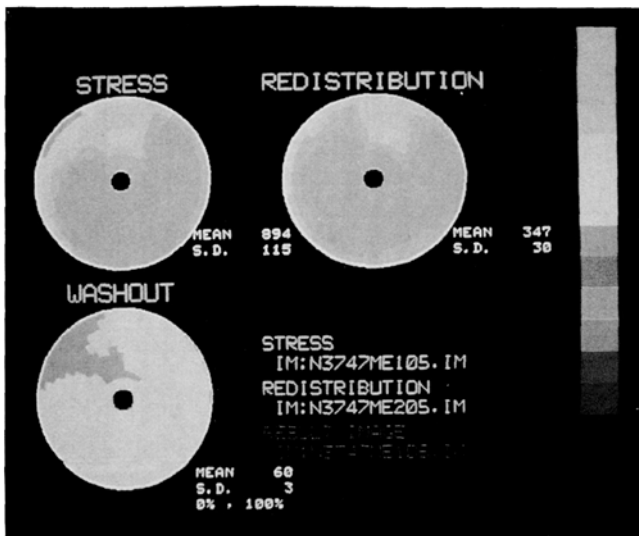


Fig. 2. Myocardial tomograms in case 14. Two-dimensional polar representations of Tl-201 myocardial stress distribution. Perfusion defect corresponds to region supplied by left anterior descending artery (*top left*). Incomplete redistribution (*top right*) and 4-h percentage washout (*lower*)

fect was observed in this study, and the defect was incompletely redistributed. The planar image obtained after the second angiography was normal.

Discussion

Coronary artery obstruction is one of the most serious cardiovascular complications of Kawasaki disease. The prognosis of patients with this disease should be carefully assessed, since the severity of the coronary lesions is not always reflected by the clinical manifestations. In fact, most of the patients in the present study remained entirely well with clinically silent disease. Even myocardial infarction may be asymptomatic in Kawasaki disease. Data on patients with myocardial infarction were collected in a nationwide survey conducted by the Japanese Kawasaki Disease Research Committee [3]. According to the results, myocardial infarction was asymptomatic in 37% of patients. Nakano et al. reported that significant clinical symptoms were recognized in only 45% of patients [4]. We experienced 18 patients with myocardial infarction. Among these, 7 (39%) were asymptomatic; and, especially among 10 patients treated with antiplatelet drugs, 7 were asymptomatic. In the one case of sudden death in our present study, because of the lack of symptoms, we had not expected this outcome, and none of the changes in the patient's coronary lesions were recognized until autopsy. It goes without saying that accurate recognition of coronary lesions by selective angiography is most important for the management of Kawasaki disease patients. However, coronary

angiography cannot be performed without risk, and some patients may suffer severe complications. Noninvasive methods for the screening of severe coronary lesions are needed before coronary angiography. Although two-dimensional echocardiography is a useful method for detecting aneurysms [5], it is ineffective for obstructive and stenotic lesions. We carried out treadmill stress testing in order to detect ischemia. However, this procedure correctly diagnosed only 27% of the coronary obstructions revealed by angiography.

Tomita et al. reported that 45% of patients with coronary stenosis revealed ischemic ST changes upon treadmill stress testing [6]. We initially considered this low figure to be the result of abundant collateral circulation in these patients. We now think it is dangerous to have such a sanguine view. Although Cumming et al. reported the Bruce treadmill protocol to be suitable for children [7], it may be insufficient for patients with ischemic heart disease. However, all patients with LMT obstruction in our study showed ischemic ST depression. Patients with Kawasaki disease must therefore be evaluated in the future using the classifications based on the coronary vessels involved.

Myocardial scintigraphy is useful for detecting the presence of myocardial ischemia. Thallium-201 myocardial tomography has been suggested to be a significant improvement over planar scintigraphy for the detection and localization of myocardial ischemia [8]. In Kawasaki disease patients examined by Kondoh et al. [9], tomography detected 86% of cases of coronary artery obstruction or stenosis, whereas planar imaging detected only about 60%.

Our evaluation using myocardial tomography proved that most patients with clinically silent coronary artery obstruction have myocardial damage. It is likely that myocardial damage may be a causative factor of arrhythmia. Although only one patient was proved to have frequent premature ventricular beats in this study, we experienced another three patients who showed some arrhythmia. All of them had a history of myocardial infarction. The cause of sudden death in fatal cases may therefore be arrhythmia. Recently, we experienced a patient with 6 complexes of ventricular tachycardia confirmed by Holter monitoring. Bilateral giant coronary aneurysms and frequent premature ventricular beats had already been demonstrated. His right giant aneurysm was strongly suspected to be obstructed, but this was not confirmed by angiography. For this reason, this patient was not included in the study group. The prognostic importance of ventricular arrhythmia in Kawasaki disease patients with coronary artery obstruction should thus be recognized. This is borne out by the findings of Holter monitoring in the above recent case.

Careful observation using these tests, especially myocardial tomography and Holter monitoring, must be done in patients with coronary artery obstruction or giant coronary aneurysm even if they are free of cardiac symptoms. One-third of giant coronary aneurysms progress to obstruction; moreover, this occurs silently in most patients, making it difficult to arrive at judgments based on clinical symptoms. However, it seems advisable to evaluate patients with giant coronary aneurysm every 3 or 4 months, and, in fact, this is our current policy.

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