Valvular Heart Disease in Kawasaki Syndrome

—Incidence and Natural History—

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Received for publication July 25, 1989

Summary: It has been reported that Kawasaki syndrome is accompanied with mitral regurgitation or aortic regurgitation in some cases. To elucidate the incidence and the natural history of valvular heart disease in Kawasaki syndrome, we analyzed the patients who were detected to have a new heart murmur after the onset of Kawasaki syndrome. From 1973 to 1988, we have experienced 13 cases with valvular heart disease in 1215 cases of Kawasaki syndrome, 12 cases with mitral regurgitation (1.0%) and one with aortic regurgitation (0.1%). Valvular lesions were confirmed by angiography or pulsed Doppler echocardiography. The age at onset of Kawasaki syndrome, the duration of fever, the maximum erythrocyte sedimentation rate, and the incidence of coronary artery lesions in these cases were compared with the same variables in 30 cases of without valvular lesion in Kawasaki syndrome. There were no statistical difference between the cases with valvular heart disease and without valvular heart disease about the age of onset (mean $\pm$ SD 10.2 $\pm$ 12.7 months vs 20.8 $\pm$ 18.4 months; N.S.) and the maximum erythrocyte sedimentation rate (87.7 $\pm$ 29.0 mm/h vs 87.2 $\pm$ 35.6 mm/h; N.S.). Whereas the duration of fever in cases of valvular heart disease was more extended than those without valvular heart disease (20.3 $\pm$ 8.1 days vs 10.3 $\pm$ 4.3 days; $p<0.001$), and the incidence of coronary artery lesions in the cases of valvular heart disease was significantly higher than those without valvular heart disease (12/13 cases vs 7/30 cases; $p<0.001$), thus suggesting that the cases of valvular heart disease were subject to a severe case of Kawasaki syndrome. All valvular heart disease appeared within 1 month after the onset of Kawasaki syndrome, except in one case whose heart murmur was noticed 5 years after the onset. The heart murmur disappeared within 2 months after the onset of valvular heart disease in 5 cases, however in another 7 cases, the heart murmur persisted more than 2 years (mean; 5.3 years to date) or one has died of acute congestive heart failure due to mitral regurgitation. All cases with persistent valvular disease revealed mitral or aortic valve prolapse. Our data suggest that the cause of valvular heart disease might be different by the time of onset and duration of valvular heart disease. Valvular heart disease of the early onset and short duration may be caused mainly by pancarditis —especially valvulitis—, valvular heart disease of early onset and persistence may possibly develop dysfunction in the valve and papillary muscle due to the sequelae of valvulitis, and valvular heart disease in late onset may be caused by ischemia. We suggest that valvular heart disease in Kawasaki syndrome may be an important cause of acquired valvular disease in children, whereas rheumatic fever has become quite rare condition now.

Key words: Kawasaki syndrome — mitral regurgitation — aortic regurgitation — valvular heart disease — valvulitis

Introduction

In children with Kawasaki syndrome, the cardiovascular sequelae that may cause sudden death or severe cardiac insufficiency are the most important clinical problems (Kato et al. 1982 and 1986; Suzuki et al. 1986; Tataru and Kusakawa. 1987). The cardiovascular sequelae are known to extend not only to coronary artery lesions but also to valvular heart diseases such as regurgitation (Hamada et al. 1973; Kato et al. 1975; Nakano et al. 1984; Suzuki et al. 1988). Mitral regurgitation and aortic regurgitation due to Kawasaki disease have been reported (Yamamoto et al. 1968; Kato et al. 1974; Hirose et al. 1975; Honda et al. 1979), and serious cases have required valve replacement (Kitamura et al. 1980; Gidding et al. 1986).

These valvular heart diseases are varied in type, ranging from mild that appears transiently in the course of Kawasaki syndrome to one that is accompanied by congestive heart failure with morbidity (Hamada et al. 1973; Akagi, 1987). Detailed studies on the incidence and the natural history of these related valvular heart diseases and the mechanisms by which they might develop are few. This report is aimed at clarifying the incidence, the clinical features and the natural course of the valvular heart diseases that develop concurrently with Kawasaki syndrome.

Subjects and Methods

From 1973 to 1988, we have experienced 1215 cases of Kawasaki syndrome patients who were followed from the acute phase in our department. Of these, 13 cases (5 female, 8 male) in which heart murmurs were discovered during the course of Kawasaki syndrome were investigated in this study. Twelve involved mitral regurgitation, and one aortic regurgitation. The

age at onset of Kawasaki syndrome ranged from 2 months to 3 years (mean 10.2 ± 12.7 months). The follow-up period was from 1 month to 16 years (mean 6.8 years). We investigated the following parameters; age, sex, duration of fever, degree of heart murmur, time of occurrence of heart murmur and its duration, presence of congestive heart failure, maximum erythrocyte sedimentation rates, electrocardiographic findings, 2-dimensional echocardiographic findings, angiographic findings, treatment, and prognosis. As to the age, sex, duration of fever and maximum erythrocyte sedimentation rate, the cases were studied in comparison with 30 matched cases with Kawasaki syndrome not complicated with any valvular heart diseases.

The duration of fever was defined as the number of days on which the maximum body temperature after the onset of Kawasaki syndrome reached 38°C or more. The time of occurrence of a heart murmur referred to the first day on which a new heart murmur was heard on auscultation after the onset of Kawasaki syndrome. The duration of the heart murmur was defined as the period during which a heart murmur was heard on auscultation. The auscultation was done by two or more pediatric cardiologists.

Two dimensional echocardiography and electrocardiography were done more than twice a week within one month after the onset of Kawasaki syndrome and once every 1-2 months from 1 month after the onset. The diameter of both sides of the coronary artery, left ventricular ejection fraction, shape of the valve and the presence or not of pericardial effusion were evaluated by 2-dimensional echocardiography. Evaluation on the valvular regurgitation was also made with pulsed Doppler echocardiography. Two dimensional echocardiography and pulsed Doppler echocardiography were performed with an ALOKA SSD-730 and SSD-860 with use of a 2 MHz

TABLE 1
Analysis of valvular regurgitation in Kawasaki syndrome

Case	Age (month)	Sex	Heart Murmur (Levine)	Fever (day)	Delay (day)	Duration (*:extant)	Max. ESR (mm/hour)
1	2	M	III/VI DM (+)	22	21		N. D.
2	3	F	III/VI DM (-)	34	24	2 years	72
3	4	F	II/VI DM (-)	18	10	6 years*	N. D.
4	4	F	III/VI DM (+)	25	18	2 months	72
5	5	M	III/VI DM (-)	20	14	2 years*	96
6	6	M	III/VI DM (+)	30	5	8 years	51
7	6	M	II/VI DM (+)	19	20	1 month	62
8	8	M	II/VI DM (-)	11	7	1 month	109
9	8	F	III/VI DM (-)	6	8	1 month	65
10	11	F	III/VI DM (+)	28	27	5 years*	131
11	28	M	I/VI DM (-)	24	16	2 months	N. D.
12	46	M	I/VI DM (-)	11	5 years	4 years*	134
13	2	M	II/VI	16	30	6 years*	85

TABLE 1
Analysis of Valvular Regurgitation in Kawasaki Syndrome (cont.)

Case	ECG Findings	DEGREE	CAL	MVP	CHF	Regimen	Prognosis
1	ST↓ (V ₅ ~V ₆)	N. D.	AN	-	+	ASA+GG	Death
2	CRBBB, ST↓ (II, III, avF)	II	GAN	-	-	ASA	Sudden Death
3	N. S.	II	AN	+	-	unknown	Alive
4	AV dissociation	II	GAN	+	+	ASA→FLB	Alive
5	LVH	IV	D	-	+	ASA+GG	Alive
6	LVH	II	GAN	+	+	steroid	Alive
7	prolonged PQ	-	GAN	-	+	ASA	Alive
8	N. S.	-	GAN	-	-	ASA	Alive
9	N. S.	N. D.	-	-	-	ASA	Alive
10	LVH	III	GAN	+	+	ASA	Alive
11	abnormal Q (II, III, aVF)	I	AN	-	-	unknown	Sudden Death
12	negative T (V ₄ ~V ₆)	-	GAN	+	-	ASA	Alive
13	LVH	II	AN	(AVP+)	-	ASA	Alive

Case 1-12=mitral regurgitation, Case 13=aortic regurgitation, Fever=duration of fever after onset of KS, Delay=time between onset of KS and onset of heart murmur, Duration=heart murmur duration time, ESR=erythrocyte sedimentation rate, DM=diastolic murmur, Prolapse=mitral or aortic valve prolapse, CHF=congestive heart failure, ECG=electrocardiography, ST=abnormal ST segment, CRBBB=complete right bundle branch block, LVH=left ventricular hypertrophy, N.S.=not significant change, DEGREE=degree of regurgitation (by angiography), N.D.=not done, CAL=coronary artery lesion, GAN=giant aneurysm (≥ 8 mm). AN=aneurysm, D=dilatation, ASA=acetylsalicylic acid (aspirin). GG=gammaglobulin, FLB=flurbiprofen, KS=Kawasaki syndrome,

or 3.5 MHz transducer in this study.

Angiography was performed after improvement was noticed in the inflammatory reaction of the acute phase. In principle, selective coronary angiography was performed using Judokins-Kato catheter sized 5.7F. Where it was difficult to do so in terms of technique, aortography was used. The case was defined as "normal" where the diameter of the coronary artery was not more than 3 mm on angiography or 2 dimensional echocardiography, as "dilatation" where the diameter was 3 mm to 4 mm, as "aneurysm" where the diameter was 4 mm to 8 mm, and as "giant coronary aneurysm" where the diameter was 8 mm or more.

For assessment of regurgitation, the right anterior oblique view of the left ventricle was used in the case of mitral regurgitation and the lateral view of aortography in the case of aortic regurgitation. The degree of valvular regurgitation was evaluated in accordance with Seller's classification (Sellers et al. 1964). When abnormal findings were noted on coronary angiography, a repeat coronary angiography was performed at 1 to 2 years later, and again at 3 to 4 years later.

Statistical analysis

Age, duration of fever, and maximum erythrocyte sedimentation rates in cases with valvular heart disease were compared with those in cases without valvular heart disease, using Student's t-test. The incidence of coronary artery lesions was compared using the exact probability test. Statistical significance was inferred when p was <0.05 .

Results

1) Clinical findings

Valvular heart disease was noted in 13 (1.1%; 5 female, 8 male) of 1215 cases of Kawasaki syndrome, 12 cases with mitral

regurgitation (1.0%) and one with aortic regurgitation (0.1%). In 10 of 13 cases, the age at onset of Kawasaki syndrome was less than 12 months, however no statistical difference was detected between cases of valvular heart disease and those without valvular heart disease (10.2 ± 12.7 months vs 20.8 ± 18.4 months, N.S.). Sex was not correlated with valvular heart disease, either.

The duration of fever was 10 days or more in all 13 cases except Case 9, and was overall statistically significantly prolonged compared with the duration of fever in Kawasaki syndrome without valvular heart disease (20.3 ± 9.1 days vs 10.3 ± 4.3 days, $p < 0.001$).

In the 12 cases demonstrating mitral regurgitation, a high-pitch regurgitant systolic murmur was heard at the apex, the degree of which was Levine II-III in 10 cases. The remaining 2 cases had a faint murmur of Levine I. A mid-diastolic murmur was also heard at the apex in 5 of the 12 cases. In the case of aortic regurgitation, a diastolic murmur of Levine II was heard with the point of maximum impulse felt in the third left intercostal space.

Valvular heart disease was determined to have occurred within 7 days of illness in 2 cases, 8-14 days of illness in 3 cases, and 15-30 days of illness in 7 cases. Twelve out of 13 cases had the onset in the acute phase within 30 days of illness. In Case 12 which had the onset in the convalescent phase, mitral regurgitation was heard simultaneously with chest pain suspected to be due to angina 5 years after development of the disease. In this case, A-C bypass was performed because of the advanced stage of a stenotic lesion in the coronary artery. Ischemia in the papillary muscle of the left ventricle was considered accountable for the valvular heart disease, since the time of manifestation of valvular regurgitation was consistent with the appearance of chest pain and since mitral

Fig. 1. Improvement of mitral regurgitation in Case 4.

Phonocardiography (above): High pitched pansystolic murmur was recognized in the acute phase (left). Heart murmur disappeared in the convalescent phase (right).

Pulsed Doppler echocardiography (below): Marked mitral regurgitation was detected in the acute phase (left), but improved in the convalescent phase (right).

Fig. 2. Angiography in Case 5 (acute phase).

Selective coronary angiography (above): Left main coronary artery showed mild dilatation, however no stenotic lesion was detected in either coronary artery.

Left ventriculography (middle): Severe mitral regurgitation was recognized. Bilateral axillary artery aneurysms were recognized (below).

Fig. 3. Phonocardiography and angiography in Case 6 (acute phase).

Heart murmur developed loud pansystolic murmur with mid-diastolic murmur from 5th day of illness (above). Left ventriculography revealed moderate mitral regurgitation (middle). Giant coronary aneurysms were detected in both coronary arteries (below).

Fig. 4. Serial phonocardiographies in Case 6.

No heart murmur was noted on 4th day of illness (left). High pitched pansystolic murmur and mid-diastolic murmur developed after that, however these heart murmurs disappeared 8 years after onset of Kawasaki syndrome.

Fig. 5. Two dimensional echocardiography in Case 10.

The long axis view of left ventricle showed increased bright echo of the anterior papillary muscle of the left ventricle (PM), and anterior leaflet of mitral valve prolapsed (MVP). The same findings of echocardiography was shown in Case 5.

valve prolapse simultaneously appeared.

Six of 13 cases showed congestive heart failure symptoms. Case 1 died of severe congestive heart failure due to mitral regurgitation. Case 5 continues to have congestive heart failure to date and is being treated with digoxin. In Case 6, Case 7, and Case 10, congestive heart failure improved and is in the convalescent phase.

Treatments administered were aspirin (30 mg/kg/day) alone in 8 cases, steroids (prednisolone; 2 mg/kg/day, 7 days) only in 1 case, aspirin (30 mg/kg/day)+gamma-globulin (200 mg/kg/day, 5 days) in 2 cases, and other treatment in 2 cases. In the present study, no difference due to therapy could be found.

2) Laboratory findings

In the 10 cases in which the erythrocyte sedimentation rate during the clinical course could be followed, the maximum

Fig. 6. Case of aortic regurgitation (Case 13).

High pitched diastolic murmur was noted at the 3rd intercostal space near the left sternal border. Two dimensional echocardiography showed aortic valve prolapse (AoV), and pulsed Doppler echocardiography demonstrated the flow of aortic regurgitation (AR).

erythrocyte sedimentation rate was 87.7 ± 29.0 mm/h, showing no significant difference from the maximum erythrocyte sedimentation rate of 87.2 ± 35.6 mm/h in those cases without valvular heart disease.

Ten of 13 cases showed a change in ECG during the clinical course. Left ventricular hypertrophy was noted in four cases—Case 5, Case 6, Case 10, and Case 13. In Case 2, Case 11, and Case 12, ischemic changes were observed. In Case 4 and Case 7, AV-dissociation and I-AV block were noted, but were transient.

In 2-dimensional echocardiographic findings, coronary artery lesions were confirmed in 12 of 13 cases (92%). The incidence of coronary artery lesions was significantly higher in those with valvular heart disease than in those without (12/13 vs 7/30, $p < 0.001$). Five cases of mitral regurgitation (Case 3, 5, 6, 10, 12) and the one case of aortic regurgitation showed valvular prolapse. Increased bright echo suggestive of ischemia in the papillary muscle was observed in 2 of the 5 cases (Case 5, 10) which showed mitral valve prolapse. In all 6 cases which showed valvular prolapse, valvular heart disease persisted for 2 years or more.

Angiography was performed in 11 cases, and coronary lesions were confirmed in all cases. Of these, 7 cases had giant coronary aneurysm of 8 mm or more in diameter (Case 2, 4, 6, 7, 8, 10, 12), 3 cases had aneurysm (Case 3, 11, 13) and 1 case dilatation (Case 5). In Case 1, coronary angiography could not be performed because the patient died in the acute phase, but 2-dimensional echocardiogram revealed aneurysms each having a diameter of 6 mm in the right and left coronary arteries. In Case 9, angiography was not performed since 2-dimensional echocardiogram showed no coronary artery lesion and since the heart murmur disappeared within 1 month of murmur onset.

In 10 cases of mitral regurgitation for which angiography of the left ventricle

was performed, we found Seller's grade IV regurgitation in 1 case, grade III in 1 case, grade II in 4 cases and grade I in 2 cases. In Case 7 and 8, the heart murmur disappeared before the angiographic examination and regurgitation was not shown by angiography of the left ventricle.

3) *Natural history*

The duration of valvular heart disease showed two patterns, one in which valvular heart disease disappeared relatively early within 2 months (5 cases) and the other in which valvular heart disease persisted over a long period of time of 2 year or more (7 cases). In 5 cases of mitral regurgitation and the 1 case of aortic regurgitation, valvular regurgitation has persisted 6 years, 2 years, 5 years, 4 years, and 6 years, to date. In Case 6, severe mitral regurgitation was noted from the acute phase, but improved after 8 years.

Three of 13 cases have died. Case 1 died of acute congestive heart failure considered attributable to mitral regurgitation on the 22nd day of Kawasaki syndrome. Case 2 and Case 11 died suddenly, having a severe stenotic lesion in the both coronary arteries concurrently. Both may have had myocardial infarctions, which led to the sudden death.

Discussion

Cases have been reported in which valvular heart diseases such as mitral regurgitation and aortic regurgitation develop concurrently in the clinical course of Kawasaki syndrome (Hamada et al. 1973; Kato et al. 1975), and valve replacement has occasionally been required (Kitamura et al. 1980; Gidding et al. 1986). However, there has been no study that deals with the incidence, clinical features, and natural course of valvular heart diseases developing concurrently with Kawasaki syn-

drome. We therefore conducted a clinical control study of cases with clearly audible heart murmur.

Of 1215 cases of Kawasaki syndrome patients, 13 cases (1.1%) showed a new heart murmur during the clinical course of Kawasaki syndrome. They involved either mitral regurgitation (12 cases; 1.0%) or aortic regurgitation (1 case; 0.1%). Our hospital takes cases referred from other hospitals. So, it is possible that ours included many serious cases among the ordinary cases of Kawasaki syndrome.

In this study, patients with valvular heart disease showed no difference from those without valvular heart disease in terms of age at onset of Kawasaki syndrome or sex. However, in 10 of 13 cases (77%) of valvular heart disease, the age at onset of Kawasaki syndrome were less than 12 months after birth. These early onset of Kawasaki syndrome may become a risk factor for progress to valvular heart disease. The duration of fever was significantly prolonged compared with Kawasaki syndrome without valvular heart disease. Such patients with valvular heart disease were serious cases of Kawasaki syndrome.

Of particular note was the fact that most of the cases with valvular heart disease had coronary lesions concurrently. Moreover, more than half of them had a giant coronary aneurysm 8 mm or more in diameter. This suggests that both coronary artery lesions and valvular heart disease are related to the severe systemic inflammation of Kawasaki syndrome.

More than 90 percent of the valvular heart disease developing concurrently with Kawasaki syndrome were mitral regurgitation and in only one case was aortic regurgitation found. Mitral regurgitation occurred at a higher incidence than aortic regurgitation presumably since it is caused not only by the impairment of the valve itself but also by impairment of the papillary muscle and myocardium. It has re-

ported that Doppler echocardiography and aortography used in the acute phase of Kawasaki syndrome revealed mitral regurgitation, tricuspid regurgitation, and aortic regurgitation at a high incidence, respectively (Nakano et al. 1984; Akagi, 1987; Suzuki et al. 1988). Most of the cases of regurgitation are so mild that they cannot be heard as heart murmurs. It was well known that mild valvular regurgitation can be detected frequently in normal subjects using Doppler echocardiography (Kostucki et al. 1986; Akasaka et al. 1987; Berger et al. 1989), so one can not neglect the possibility that some of the mild valvular regurgitation which was noted in the acute phase of Kawasaki syndrome have included "physiological" valvular regurgitation. In this study, this "inaudible" valvular regurgitation was not included. Mild inaudible valvular regurgitation perhaps occurs with high incidence rate in the acute phase of Kawasaki syndrome, but is mostly subclinical and may pose no problem clinically.

In 5 of 12 cases in which clinical observation could be made, valvular heart disease improved spontaneously within two months, but in 7 cases it persisted for 2 years or more. In the 6 cases in which valvular heart disease persisted over a long period, the heart murmur disappeared about 8 years after the onset of the disease. As described above, in some cases, valvular heart disease in Kawasaki syndrome disappears spontaneously, as may the coronary aneurysms. Where valvular heart disease persists over a long period of time, it is often accompanied by changes in the valve and supporting tissue such as mitral or aortic valve prolapse and increased echobrightness of the papillary muscle on 2-dimensional echocardiography.

Valvulitis or myocarditis arising from pancarditis and papillary muscle dysfunction due to stenosis or occlusion of the coronary artery are considered to be the

mechanism by which valvular heart disease in Kawasaki syndrome develops. Several cases of mitral regurgitation or aortic regurgitation caused by Kawasaki syndrome have been reported to occur without the association of coronary artery lesions, and autopsy findings in some of those cases have confirmed the inflammatory changes in the mitral or aortic valve tissues (Hamada et al. 1973; Imakita et al. 1984). Other papers suggested that according to pathologic studies of autopsy specimens, pancarditis is most frequent during the acute phase, in which situation valvulitis might be expected to develop primarily or as a result of myocarditis or endocarditis (Fujiwara and Hamashima, 1978).

Results of our present study suggest that the mechanism of valvular heart disease differs according to the time of onset and duration of disease, since (1) the time of onset can be divided into the acute phase (within 1 month) and the late phase (after 1 month), and (2) since changes in the valve and its supporting tissue are noted in cases in which valvular heart disease persists over a long period of time. That is, valvular heart disease which develops in the acute phase and improves early can possibly be attributable mainly to pancarditis such as valvulitis. Valvular heart disease which occurs in the acute phase and persists over a long period of time may possibly develop dysfunction in the valve and papillary muscle due to the sequelae of valvulitis or a stenotic lesion in the coronary artery. Valvular heart disease occurring in the late phase may be caused by ischemia in the papillary muscle resulting from coronary stenosis.

In the present study, 3 of 13 cases died. Two cases involved sudden death probably due to myocardial infarction and 1 case died of acute heart failure resulting from valvular heart disease. Since most patients with valvular heart disease have a severe lesion in the coronary artery in addition

to valvular regurgitation, a careful follow-up is needed even when valvular regurgitation improves.

Treatment of valvular heart disease consists of a regimen using chiefly digitalis preparations for congestive heart failure and surgical treatment based mainly on valve replacement. We have up to the present time had no experience with valve replacement. Valvular heart disease in Kawasaki syndrome improves spontaneously in some cases. So, care should be exercised in applying valve replacement to patients other than those who have severe congestive heart failure.

We suggest that (in contrast to, for example, rheumatic fever, that is rare now) Kawasaki syndrome may be an important cause of acquired valvular heart disease in children.

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