Dilated coronary arterial lesions in the late period after Kawasaki disease

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Objectives: There are two types of late coronary dilated lesions after Kawasaki disease: new aneurysms and expanding aneurysms. The development of coronary dilated lesions late after Kawasaki disease was investigated.

Methods: Between 1978 and 2003, 562 patients with coronary arterial lesions underwent selective coronary angiography on at least two occasions.

Results: Of the 562 patients studied, 17 new dilated or expanding lesions were found in 15 patients (3%, 11 boys, four girls). The time of detection of new aneurysms after Kawasaki disease ranged from 1.9–19.2 years (median 11.4 years) and their diameters ranged from 2.0–6.5 mm (median 4.4 mm). Thirteen new aneurysms occurred in vessels in which previous aneurysms had regressed and all new aneurysms were associated with localised stenosis. A new aneurysm at the bifurcation or in the branches was seen in 14 (93%) and 13 were eccentric (87%). Of two expanding aneurysms, one involved the right coronary artery in one patient and the other the left anterior descending coronary artery. One expanding aneurysm increased from 4.4 mm to 19.5 mm over 17 years, and the other expanding aneurysm increased from 10 mm to 15 mm in one year.

Conclusions: Neither new nor expanding aneurysms have caused cardiac events. New aneurysms often develop as a pre-stenotic or post-stenotic dilatation secondary to localised stenosis. New and expanding aneurysms may be caused by haemodynamic factors in addition to the abnormality of the coronary arterial wall after severe acute vasculitis. Coronary arterial wall abnormalities were stenosis as well as, rarely, dilatation of the vessels in the late period. It is important to recognise that the changes of the coronary arterial wall persist late after regression of a large aneurysm.

The vasculitis of Kawasaki disease (KD) causes coronary aneurysms in about 10% of patients early after the onset.¹ Aneurysms usually change their shape after the acute phase, but some may persist for years whereas others either regress or evolve into stenotic lesions.^{2–4} Usually, the diameters of persistent aneurysms may increase slightly because of somatic growth or they may decrease because of intimal thickening of the vascular wall.^{5–8} In the late period of KD either new aneurysms or expanding aneurysms are unusual but have been reported.^{9–12} We investigated the characteristics of the dilated lesions and their time of appearance and speculate about their cause.

PATIENTS AND METHODS

Between 1978 and 2003, after giving informed consent, 562 patients with coronary arterial lesions underwent selective coronary angiography on at least two occasions. The protocol was as follows. Coronary angiography for patients with coronary arterial lesions was performed immediately after the acute phase of KD. All patients underwent a second coronary angiography after one year and subsequent follow up coronary angiography was done at 3–5 year intervals depending on the findings. If the aneurysms regressed, subsequent coronary angiography was not done but the patients were followed up in the outpatient clinic by non-invasive imaging including echocardiography and electron beam computed tomography. If coronary arterial lesions were suspected on non-invasive imaging, coronary angiography was considered at that time. Some patients who attended our hospital late after the acute KD episode were also included. Those patients did not undergo coronary angiography immediately after the acute phase.

RESULTS

We found 17 lesions in 15 patients that were coronary dilatations developing late after KD (3%, 11 boys, four girls). All 15 had received anticoagulant treatment. Eight patients underwent coronary artery bypass grafting (CABG), and one patient underwent percutaneous balloon angioplasty. Late coronary artery dilatations after KD can be divided into two groups: new aneurysms and expanding aneurysms.

New aneurysms

We found 15 new aneurysms in 13 patients in the coronary arteries as follows: right coronary artery (RCA), three; left anterior descending coronary artery (LAD), eight; left circumflex artery, three; and left main trunk, one. Fourteen of 15 new aneurysms were in the proximal vessel segments. In 10 lesions, there had been a pre-existing aneurysm at the same site in the initial coronary angiography. Pre-existing aneurysms had been detected by echocardiography in the acute phase for three lesions. Acute stage status for the two remaining new aneurysms was unknown. The diameter of all pre-existing aneurysms exceeded 7 mm.

The age at onset of KD ranged from 3 months to 7.0 years (median 15 months). The interval from the onset of KD to the latest coronary angiography ranged from 4.4–22.1 years (median 12.5) and the time of first detection of new aneurysms ranged from 1.9–19.2 years (median 11.4 years) (table 1). The interval from the onset of KD to the first

Abbreviations: CABG, coronary artery bypass grafting; KD, Kawasaki disease; LAD, left anterior descending coronary artery; RCA, right coronary artery

Table 1 Characteristics of the new aneurysms

Age (years)	Sex	Interval from KD (months)	Segment	Diameter (mm)	LS (%)	Pre-existing aneurysm	Branching or bifurcation location	Eccentric
1.9	M	1.5	LCX 15	4.1	90	Yes	Branch	No
4	M	3.7	LAD 6	2.0	75	Yes	Branch	Yes
7	F	6.2	RCA 2	3.0	90	Yes	Branch	Yes
10	F	9.8	LAD 6	5.2	90	Yes	Branch	Yes
11	M	4.4	RCA 1	4.2	75	Yes	Branch	Yes
12	F	10.2	LAD 6	4.7	90	Yes	Branch	Yes
5	M	4.3	LMT 5	3.8	75	Yes	No	No
14	M	13	LAD 6	4.4	50	Yes	Branch	Yes
14	M	13	RCA 1	4.9	75	Yes	Branch	Yes
12	M	12	LAD 6	6.5	50	Unknown	Branch	Yes
17	F	16	LCX 11	2.5	25	Yes	Branch	Yes
17	F	13	LAD 6	5.4	25	Yes	Branch	Yes
7	M	6.2	LAD 6	5.1	50	Yes	Bifurcation	Yes
11	M	9.9	LCX 13	3.2	90	Unknown	Bifurcation	Yes
19	M	15.8	LAD 6	5.6	25	Yes	Bifurcation	Yes

F, female; KD, Kawasaki disease; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LMT, left main trunk; LS, localised stenosis; M, male; RCA, right coronary artery

detection ranged from 1.6–16.3 years (median 9.9 years). The time of the first appearance of localised stenosis $\geq 25\%$ ranged from 1.0–16.3 years (median 5.4 years). In five lesions a new aneurysm and localised stenosis first appeared at the same time. For the remaining eight lesions the interval from the first appearance of localised stenosis to the appearance of new aneurysms ranged from 0.6–6.4 years (median 3.3 years).

The diameter of the new aneurysms ranged from 2.0–6.5 mm (median 4.4 mm). In nine of 11 lesions on follow up coronary angiography, the diameter of the new aneurysms was slightly increased, the increase ranging from 0.4–2.3 mm. After CABG, one new aneurysm with a diameter of 2.0 mm resolved, whereas the diameter of the other new aneurysm decreased slightly.

All new aneurysms had associated localised stenosis. The degree of stenosis was 25% in three patients, 50% in three, 75% in four, and 90% in five. Twelve lesions were post-stenotic and three pre-stenotic (table 1). A new aneurysm at the bifurcation or in the branches was seen in 14 patients (93%) (fig 1). In this study, branches referred to the small branching vessels from the major branches. Bifurcation referred to the bifurcation between the LAD and the diagonal branch or the bifurcation between the posterolateral and posterodescending branch. Thirteen new aneurysms were eccentric. None of the new aneurysms caused cardiac events, although the coronary artery of some patients was revascularised.

Three cases of new aneurysms

One girl developed KD when 4 months old. Giant aneurysms were seen on the RCA and the left coronary artery by two dimensional echocardiography. At coronary angiography four months after the onset the left coronary artery the aneurysm was smaller. An angiogram recorded seven years after the onset showed a 50% localised stenosis in the LAD and occlusion of the RCA (fig 2). She had not experienced chest pain. Ten years after the onset there was a new aneurysm with associated 90% localised stenosis in the LAD. The pressure gradient estimated by the velocity at the localised stenosis by two dimensional echocardiography was 31 mm Hg (fig 3). She underwent a CABG to the LAD. One year later the estimated pressure gradient was 4 mm Hg at the same lesion. The diameter of the new aneurysm decreased from 5.2 to 4.5 mm.

A boy had KD at the age of 15 months. Although he had severe heart failure he did not undergo coronary angiography at the time. An angiogram five years after the acute episode showed segmental stenosis in the RCA. Twelve years after the onset there was a new aneurysm with associated 50% localised stenosis in the LAD. Seven years later the findings were almost the same, although the aneurysm was slightly larger (fig 4). Figure 5 shows the intravascular ultrasound findings in the new aneurysm. In the proximal portion of the aneurysm intimal thickening was severe, in the aneurysm itself it was slight, and distally eccentric intimal thickening was detected.

Figure 1 New aneurysm at bifurcation. Angiograms at (left) 8 years and (right) 7 years.

Figure 2 New aneurysm with severe localised stenosis that developed as a post-stenotic dilatation. Angiograms at (top) 2 years, (middle) 7 years, and (bottom) 10 years. The angiogram showed a new aneurysm with severe localised stenosis.

Another boy had KD at the age of 5 months. Two months after the onset angiograms showed aneurysms of the RCA and the LAD. Nine years after the acute illness an angiogram showed a 50% localised stenosis in the RCA. At 14 years there was a new aneurysm with 75% localised stenosis in the RCA and a new aneurysm with 25% localised stenosis in the LAD (fig 6).

Expanding aneurysms

Two expanding aneurysms were found, one in segment 1 of the RCA and the other in segment 6 of the LAD. One aneurysm of the RCA had decreased from 7.8 mm to 4.4 mm a year after its onset but subsequently enlarged to 19.5 mm over the next 17 years (fig 7). The other patient with an expanding aneurysm had KD when 11 years old. The

Figure 3 Pressure gradient at localised stenosis estimated by Doppler echocardiography. (Top) Echocardiogram before coronary artery bypass grafting (CABG) at 10 years. The velocity at the localised stenosis was 2.8 m/s. (Bottom) Echocardiogram after CABG. The velocity at the localised stenosis was 1.0 m/s.

Figure 4 New aneurysm related to branching portion. Angiograms at (top) 5 years, (middle) 2 years, and (bottom) 19 years.

Figure 5 Intravascular ultrasound findings of a new aneurysm.

Figure 6 New aneurysm that developed as a pre-stenotic dilatation. Angiograms (top) two months, (middle) nine years, and (bottom) 14 years after onset.

Figure 7 Angiographic follow up of an expanding aneurysm in a patient who had Kawasaki disease at the age of 18 months. Angiograms at (A) age 22 months (aneurysm diameter 7.8 mm), (B) 2 years 9 months (4.4 mm), (C) 10 years (9.6 mm), (D) 14 years (16.3 mm), and (E) 20 years (19.5 mm).

aneurysm increased from 10 mm to 15 mm in one year. Localised stenosis was not present in the two cases of expanding aneurysms and both patients were asymptomatic.

DISCUSSION

We found that new aneurysms developed in the same location at which there had been a pre-existing aneurysm. New aneurysms were aneurysms that redeveloped after previous regression. All pre-existing aneurysms were large and we hypothesised that the structure of the coronary arterial wall was irreversibly damaged by the severe acute inflammation. Most new aneurysms were associated with the appearance of severe localised stenosis. The pressure gradient generated by severe localised stenosis causes abnormal blood flow profiles, and these haemodynamic abnormalities exacerbate the existing damage from severe vasculitis. New aneurysms related to severe localised stenosis may be caused by pre-stenotic or post-stenotic dilatation. Furthermore, haemodynamic factors at the bifurcation and branches may predispose patients without severe localised stenosis to irregularity of the coronary wall. The wall properties at the bifurcation and branches may also favour aneurysm formation, as histologically the wall at a branching point is different from walls in other locations.¹²

Usually, the remodelling of localised stenosis after a large aneurysm caused by KD comprises severe intimal thickening.³⁻⁸ It was thought that the coronary arterial wall of localised stenosis consisted of intimal thickening after regression of a large aneurysm; however, in this study the coronary arterial wall abnormalities late after KD were not only stenosis but also dilatation of the vessels, although such development was rare. Dilated coronary arterial lesions in the late period after KD indicated that the coronary arterial wall was irregular late after acute vasculitis. Although the cause is unknown, a small, weak portion in the thickened and firm wall may develop in the damaged coronary arterial wall after severe vasculitis caused by KD. The weak portion may be related to branching and may be dilated by the haemodynamic force of severe localised stenosis.

As most new aneurysms first appear during adolescence, growth of the coronary artery in relation to rapid somatic growth may also be a factor in causing new aneurysms. We must realise that the abnormality of the coronary arterial wall after regression of a large aneurysm consists not only of a thickened and firm portion but also a portion of partial thinning and weakness. This finding is useful for percutaneous coronary intervention, CABG, and long term follow up of patients with a history of a large aneurysm caused by KD.

Similarly, we believe that abnormalities of the coronary arterial wall contribute to the development of expanding aneurysms. Expanding aneurysms are proximal and subject to similar strong haemodynamic forces as is the aorta.¹³

The prevalence of dilated lesions in adult atherosclerosis and the occurrence of new aneurysms in cerebral aneurysms have been reported with a suggested incidence of 0.3–4.7%.¹³⁻¹⁸ Haemodynamic factors, including hypertension, bifurcation wall characteristics, and weakening of the wall by atherosclerosis, were cited as causes. Some of these factors may also be common to the dilated coronary arterial lesions late after acute KD.

All new aneurysms were small or of medium size and, in our experience, neither new nor expanding aneurysms have led to clinical events. However, a patient with a new aneurysm and severe localised stenosis leading to occlusion has been reported on, although he remained asymptomatic.¹¹ The occurrence of cardiac events depends on the degree of localised stenosis. On the other hand, if a new aneurysm occurs in some cases, the progression of localised stenosis must be anticipated. A patient with an expanding aneurysm

who was operated on to prevent rupture has also been reported on.¹² Acute myocardial infarction secondary to a large aneurysm certainly is possible. Such patients must be followed up closely and be given anticoagulants.

We emphasise the abnormalities of the coronary arterial wall in the appearance of new aneurysms. Therefore, although some of the new aneurysms were small, we called them “aneurysms” in this study on the basis of their shape. We must not ignore the abnormality of the coronary wall after apparent regression of a large aneurysm to prevent cardiac events in the future. Furthermore, we must develop a better understanding of long term changes in the vascular wall after severe acute vasculitis of KD.

Conclusion

New aneurysms and expanding aneurysms imply that the coronary arterial wall is abnormal late after previous regression. We suspect that new and expanding aneurysms result from haemodynamic factors in addition to partial weakening of the coronary wall late after acute severe vasculitis.

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