

# Cardiac Sequelae in Recurrent Cases of Kawasaki Disease: A Comparison Between the Initial Episode of the Disease and a Recurrence in the Same Patients

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**ABSTRACT.** *Objective.* Cardiac sequelae develop more frequently after recurrent Kawasaki disease than from the initial onset of the disease. The purpose of this study was to observe the existence of the sequelae at the initial and second onsets of the disease simultaneously with a large cohort.

*Materials and Methods.* From the database of patients with Kawasaki disease prepared by the Japanese Kawasaki Disease Research Committee, 559 cases with recurrences recorded between 1989 through 1994 and their initial occurrence listed in the database were selected. Their proportions of cardiac sequelae after the initial and second onsets of Kawasaki disease were compared.

*Results.* Of the 68 patients with cardiac sequelae after the initial onset, 32 (47%) suffered the sequelae after the second onset, whereas 78 (16%) of the 491 who were without cardiac sequelae after the initial onset developed the sequelae after the recurrence. Both proportions were higher than proportions in all patients with Kawasaki disease. In addition to the sex (male) and the existence of the sequelae after the initial onset, age at the second onset (older age) and the interval between the two episodes (longer period) were suspected to be risk factors for sequelae attributable to recurrent Kawasaki disease.

*Conclusion.* Linked data of the initial and second episodes of Kawasaki disease showed that the risk of developing cardiac sequelae attributable to recurrent Kawasaki disease is high among both those with and without the sequelae at the initial episode. *Pediatrics* 1998;102(6). URL: <http://www.pediatrics.org/cgi/content/full/102/6/e66>; *mucocutaneous lymph node syndrome, recurrence, cardiac sequelae, risk factors.*

Cardiac sequelae attributable to Kawasaki disease constitute one of the serious problems associated with the disease,<sup>1</sup> and their risk factors have been discussed.<sup>2,3</sup> One of the interesting features of the disease is its recurrence.<sup>4,5</sup> Nationwide surveys of the disease in Japan showed that the disease recurs in ~3%.<sup>6,7</sup> Some have reported the relationship between the cardiac sequelae and the recurrence of Kawasaki disease, but the data from the Japanese nationwide survey were used in only one study, which examined the aforementioned relationship in a large population.<sup>8</sup> The study showed

that cardiac sequelae occur more frequently after a recurrence of Kawasaki disease than after the initial episode. However, the study had a disadvantage: it compared the proportion of the sequelae only between the patient group with the initial episode of the disease and the group with recurrent attacks, but no linkage between the first and second episodes was conducted.

In this study, data from the nationwide epidemiologic surveys on patients with recurrent Kawasaki disease are provided to elucidate the details of the development of cardiac sequelae at the initial and second episodes.

## MATERIALS AND METHODS

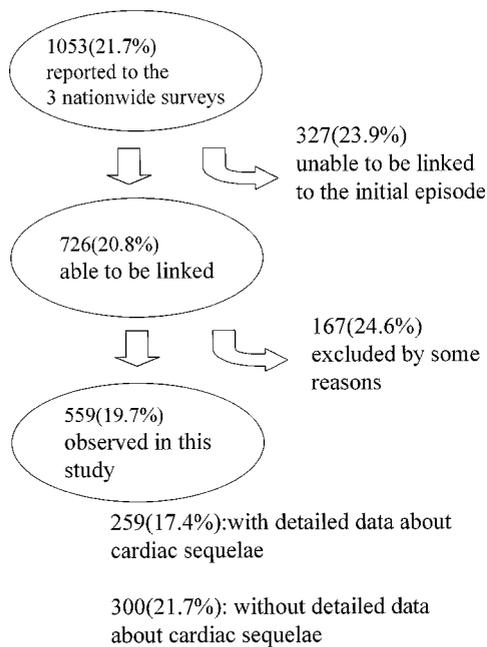
The Japanese Kawasaki Disease Research Committee has a database of 128 306 patients in Japan with Kawasaki disease. All the patients were reported in the 13 nationwide surveys of the disease conducted by the committee. From this database, 1053 recurrent cases reported in the three most recent surveys were selected. The 11th, 12th, and 13th surveys were conducted for patients diagnosed between 1989 and 1990,<sup>9</sup> 1991 and 1992,<sup>10</sup> and 1993 and 1994,<sup>7</sup> respectively.

We tried to link these data of 1053 recurrent cases and 128 306 cases, using the date of birth and sex, after which we identified the patients by name. Of the 1053 recurrent cases, 327 could not be linked because some were not registered by name; 57 were excluded because this was the third (54 cases) or fourth (3 cases) recurrence; and 41 were suffering from reexacerbation of the disease but not recurrence (because the interval between the onsets of the two episodes was within 2 months<sup>5</sup>). Other reasons, such as no data on cardiac sequelae collected in the nationwide surveys at the initial onset, excluded 36 cases, and an additional 30 patients were excluded because they visited the hospital on or after the 15th day from the onset of illness. Consequently, data for 559 cases were eligible for the analyses (Fig 1).

For the 559 cases observed, the following data were obtained from the nationwide survey database: the date of birth; sex; and information on the disease for the initial and second episodes such as date of onset, treatment, and presence (or absence) of cardiac sequelae. Age at onset and the interval between the two episodes were calculated using these data. Cardiac sequelae were defined in the nationwide surveys as one of the following findings after a 1-month period from onset: coronary aneurysms including dilatation, coronary stenosis including narrowing, myocardial infarction, and valvular lesions.<sup>7,11,12</sup> In addition, the 12th and 13th surveys had detailed data on whether an individual patient had each of the sequelae noted above.<sup>6</sup> In Japan, giant coronary aneurysms are defined as those with a diameter of  $\geq 8$  mm, measured on two-dimensional echocardiography and/or coronary angiography.<sup>13</sup>

First, we observed the relationship between the initial and second episodes in relation to cardiac sequelae by factors such as sex, age at initial episode, and interval between the two episodes. Second, each type of sequela (such as giant coronary aneurysms, coronary aneurysms including dilatation, coronary stenosis in-

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**Fig 1.** Methods to select study items, number of patients, and percentages (in parentheses) of patients with cardiac sequelae at the second episode, by group.

cluding narrowing, myocardial infarction, and valvular lesions) was analyzed for the 259 cases on which detailed data were available (the data were required for the 12th and succeeding surveys). Next, the odds ratios with 95% confidence intervals for the cardiac sequelae in the second episode were calculated with unconditional logistic models, using the LOGISTIC procedure of SAS.<sup>14</sup> Finally, to assess a selection bias attributable to the exclusion, we examined the proportion of cardiac sequelae of 494 recurrent cases that had been excluded.

## RESULTS

The distributions of age at the initial and second onsets and the interval between the two episodes of the 559 cases (333 males and 226 females) are shown in Table 1. The average interval between the two episodes was 1.78 years.

Table 2 shows the development of cardiac sequelae for each episode. Overall, 68 (12.2%) of the 559 patients developed cardiac sequelae at the initial episode, and 32 (41.7%) of the 68 also experienced the sequelae after the second episode. On the other hand, 78 (15.9%) of the 491 that did not have the sequelae at the initial episode developed them at the second episode. This figure of 15.9% is higher than the corresponding recent figure (12.8%) for the overall patient population with Kawasaki disease in Japan.<sup>7</sup> Similar results were observed in the analyses by sex and age. Males with Kawasaki disease are more likely to develop cardiac sequelae than are females.<sup>7</sup>

**TABLE 1.** Means and Standard Deviations for Age and Interval Between the Initial and Second Episodes of Kawasaki Disease, by Sex

	All Patients (n = 559)	Males (n = 333)	Females (n = 226)
Age at initial episode (y)	1.85 ± 1.34	1.73 ± 1.30	2.02 ± 1.39
Age at second episode (y)	3.63 ± 2.04	3.43 ± 1.99	3.92 ± 2.07
Interval (y)	1.78 ± 1.56	1.70 ± 1.56	1.90 ± 1.56

**TABLE 2.** Proportion of Patients With Cardiac Sequelae of Kawasaki Disease According to the Episode, by Sex, Age at Initial Episode, and Interval Between the Two Episodes

	Cardiac Sequelae at Initial Episode		Cardiac Sequelae at Second Episode*	
	+	-	+	-
All cases	68	491	32 (47) 78 (16)	36 (53) 413 (84)
Sex				
Male	48	285	22 (46) 55 (19)	26 (54) 230 (81)
Female	20	206	10 (50) 23 (11)	10 (50) 183 (89)
Age at initial episode (y)				
<1	31	151	15 (48) 24 (16)	16 (52) 127 (84)
1-2	29	253	15 (52) 40 (16)	14 (48) 213 (84)
3+	8	87	2 (25) 14 (16)	6 (75) 73 (84)
Interval between the 2 episodes (y)				
<1	27	201	15 (56) 22 (11)	12 (44) 179 (89)
1	14	131	8 (57) 25 (19)	6 (43) 106 (81)
2+	27	159	9 (33) 31 (20)	18 (67) 128 (80)

\* Percentages are in parentheses.

This tendency also was observed in the development after the initial episode and after the second episode in those who did not experience the sequelae after the initial episode. However, among those with cardiac sequelae after both the initial and the second episodes, the proportion was nearly equal in males and females (45.8% and 50.0%, respectively). Among those who developed the sequelae for the first time after the second episode, such a development was more likely when the disease returned after ≥1 year in comparison with those with a recurrence within 1 year. Age at the initial onset did not affect the risk of development of the sequelae at the second episode.

The results of analyses on 259 cases that were reported in the 12th and 13th surveys (when detailed data on sequelae were recorded) are shown in Table 3. Of the 231 patients without sequelae at the initial episode, 27 developed coronary aneurysms (2 with giant aneurysms). Of the 22 patients with coronary aneurysms at the initial episode, the incidences were reported in 13 after the second episode. Interestingly, 4 patients had giant coronary aneurysms at the second episode: 2 had giant aneurysms also at the initial episode, whereas the other 2 were free from the sequelae at the initial onset.

The results of logistic regression analyses are shown in Table 4. Sex and the existence of cardiac sequelae at the initial episode were significant risk factors for development of the sequelae at the second episode. Moreover, a longer interval between the two episodes and an older age group at the second episode were suspected risks, even though they were not significant. The results of the multiple logistic analysis that included all of the factors were comparable with those obtained from the crude analyses.

For this study, only 559 cases of recurrent Kawasaki disease were selected from 1053 patients re-

**TABLE 3.** Kinds of Cardiac Sequelae at the Initial and Second Episodes\*

Initial Episode		Second Episode	
Kind of Cardiac Sequelae	No.	Kind of Cardiac Sequelae	No. (%)
Without cardiac sequelae	231	Without cardiac sequelae	204 (88.3)
		Giant aneurysm + stenosis	1 (0.4)
		Giant coronary aneurysm	1 (0.4)
		Coronary aneurysm	25 (10.8)
Giant coronary aneurysm + coronary stenosis	1	Aneurysm + stenosis	1
Giant coronary aneurysm	4	Giant coronary aneurysm	2
		Aneurysm + stenosis	1
		Coronary aneurysm	1
Coronary aneurysm + valvular lesion	1	Coronary aneurysm	1
Coronary aneurysm	21	Without cardiac sequelae	9 (42.9)
		Coronary aneurysm	12 (57.1)
Valvular lesion	1	Without cardiac sequelae	1
Total	259	Without cardiac sequelae	214 (82.6)
		Giant aneurysm + stenosis	1 (0.4)
		Giant coronary aneurysm	3 (1.2)
		Aneurysm + stenosis	2 (0.8)
		Coronary aneurysm	39 (15.1)

\* Analysis involves the 259 cases for which information about the types of cardiac sequelae at both episodes was recorded in the database. Coronary artery aneurysms include dilatation; coronary artery stenosis includes narrowing. Among the 259 cases, none of the patients had myocardial infarction, at either the initial or the second episode.

**TABLE 4.** Odds Ratios With 95% Confidence Intervals for Cardiac Sequelae at the Initial Episode

	Odds Ratio (95% Confidence Interval)	
	Crude	Adjusted
Sex		
Male	Reference	Reference
Female	0.57 (0.36–0.89)	0.59 (0.37–0.95)
Age at initial episode (y)		
0	Reference	Reference
1–2	0.89 (0.56–1.41)	0.96 (0.55–1.67)
3+	0.74 (0.39–1.41)	0.82 (0.35–1.90)
Intravenous gamma globulin therapy at the initial episode		
–	Reference	Reference
+	0.88 (0.55–1.40)	0.91 (0.55–1.50)
Cardiac sequelae at the initial episode		
–	Reference	Reference
+	4.71 (2.76–8.03)	4.61 (2.67–7.97)
Age at second episode (y)		
0	Reference	Reference
1–2	1.47 (0.48–4.45)	1.55 (0.46–5.27)
3+	1.52 (0.51–4.53)	1.72 (0.43–6.97)
Interval between the two episodes (y)		
0	Reference	Reference
1	1.52 (0.90–2.57)	1.53 (0.85–2.74)
2+	1.41 (0.86–2.32)	1.27 (0.63–2.56)

ported in the 11th through 13th nationwide surveys, therefore, selection bias may have distorted the results. To evaluate any bias, we compared the proportion of cardiac sequelae at the second episode between the patient group of this study and those who were excluded. The proportions were similar among the groups (Fig 1).

## DISCUSSION

In this study, we have shown that in approximately half of the cases with cardiac sequelae at the initial episode of Kawasaki disease, the sequelae existed after the second episode of the disease. In ad-

dition, even among those patients without cardiac sequelae at the initial episode, the risk of development is greater than that for the overall patient population with Kawasaki disease.

In the nationwide surveys of the disease, cardiac sequelae are defined as specific cardiac findings 1 month after the onset.<sup>11,12</sup> In approximately half of the recurrent cases with the sequelae at the initial episode, the sequelae did not exist after the second episode. This fact indicates that more than half of the sequelae, which existed at least 1 month after the onset of initial episode, were no longer present. It is well known that some coronary aneurysms attributable to Kawasaki disease regress,<sup>1,15–17</sup> and the current results corroborate this. Even in three of the five cases with giant aneurysms at the initial episode did size decrease, and the aneurysms became small or medium-sized at the second episode.

On the other hand, the other half of patients with the sequelae at the initial episode had the sequelae after the second episode as well, a finding that is also plausible. Host factors, ie, susceptibility to vasculitis attributable to Kawasaki disease, may exist because only ~10% to 15% of the patients develop the sequelae,<sup>7</sup> and half of these had them again if they recur.

Compared with the total patient population with Kawasaki disease in Japan, the recurrence of the disease is more likely to include the development of cardiac sequelae whether or not the sequelae were present at the initial episode. This finding is plausible because repeated assaults by vasculitis associated with Kawasaki disease are more likely to have greater effect than would an isolated assault.<sup>8</sup>

Giant coronary aneurysms are the most serious outcome of Kawasaki disease. The relationship between the initial and second episodes for the development of coronary aneurysms is interesting (Fig 2). None of the small or medium-sized coronary aneurysms, including coronary dilatation, at the initial episode progressed to a giant aneurysm at the second episode. For the 2 patients with giant aneurysms

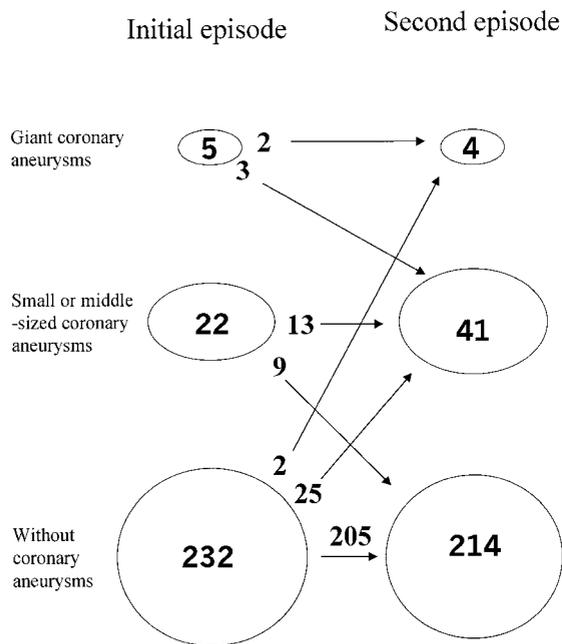


Fig 2. Relationship between changes in the coronary arteries attributable to the initial and second episodes of Kawasaki disease.

at both the initial and second episodes, it is certain that the giant aneurysms at the initial episode continued to endure until the second episode, even though they might have become smaller between the two episodes, and grew to become giant aneurysms again at the second episode. The other 2 patients with giant aneurysms at the second episode did not have them at the first episode. In other words, small or medium-sized coronary aneurysms seen in the 22 patients at the initial episode did not progress to become giant aneurysms when the disease returned. These results indicate that giant aneurysms attributable to recurrent Kawasaki disease are those that have existed since the initial episode or had developed without any sign at the initial episode.

Risk factors for the sequelae at the second episode of Kawasaki disease are male sex and the existence of the sequelae at the initial onset. Our findings substantiated this. In addition, it was suspected that a long interval between the two episodes and older age at the second episode were risk factors, even though they were not proven to have statistical significance. If a patient experiences a recurrence of Kawasaki disease long after the initial episode, the patient will have advanced to an older age group. For example, if the interval between the two episodes is 5 years, the patient must be at least 5 years old. Thus, the two factors relate to each other. The multiple logistic analysis, however, showed that the two factors might affect the existence of the sequelae at the second episode independently. According to the nationwide surveys in Japan, cardiac sequelae are more common among those  $\geq 5$  years old,<sup>7</sup> thus, older age is a risk factor not only for cardiac sequelae attributable to recurrent Kawasaki disease but also for all sequelae attributable to the disease. On the other hand, we have no theory to link the proportional

increase in the probability for the existence of the sequelae with the prolongation of the interval between the two episodes.

This study has limitations. By using epidemiologic survey data, information that could be obtained on the two episodes was limited, and no information on what might have happened between the episodes was available. Therefore, we are not able to provide answers to some interesting questions, such as the persistence or state of a cardiac sequela at some time between the two episodes or whether there was an improvement at the second episode when it existed in both the initial and second episodes. In addition, there is no information on whether the coronary aneurysms at the second episode were in the same or different arteries. Despite the limitations, however, the sample size was large enough to permit the present observation to be made.

Another drawback was a possibility of selection bias. For some reasons, complete data linkage was not possible, or some data were not available; therefore, only 559 (53.1%) of 1053 cases were available for examination. However, proportions of cardiac sequelae at the second episode were similar in the selected group and in the overall patient population (Fig 1). The effect of the bias was minimal, if it existed at all.

In conclusion, linking the data for initial and second episodes of Kawasaki disease has shown that the risk of cardiac sequelae attributable to recurrent Kawasaki disease is high both in those with and in those without the sequelae at the initial episode.

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