Recurrent Kawasaki disease and cardiac complications: nationwide surveys in Japan

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ABSTRACT

Introduction Based on data obtained before high-dose (2 g/kg) intravenous immunoglobulin (IVIG) therapy prevailed in Japan, children with a history of Kawasaki disease (KD) were highly susceptible to disease recurrence and more likely to develop cardiac sequelae. We aimed to examine the epidemiological features of cardiac complications among patients with recurrent KD following the widespread use of high-dose IVIG therapy.

Design Two cohorts of patients with recurrent KD retrieved from Japanese nationwide surveys (previous cohort: 1989–1994; recent cohort: 2003–2012) were compared.

Results Of 1842 patients with recurrent KD in the recent cohort, 3.5% and 5.2% developed cardiac sequelae at the initial and second episodes, respectively, which were markedly decreased compared with those (>10%, respectively) in the previous cohort. Multivariate analyses showed that the risk factors for cardiac sequelae at the second episode were similar between the cohorts. Patients with recurrent KD in both cohorts were more likely to have coronary aneurysms at the second episode than at the initial episode. However, when patients with coronary aneurysms at the initial episode were excluded from analyses, the difference in the proportions of coronary aneurysms between KD episodes disappeared in the recent cohort. Residual rates of previously formed coronary aneurysms were similar between the cohorts (approximately 50%).

Conclusion This study suggests that KD recurrence is no longer a risk factor for developing cardiac complications, unless cardiac sequelae appear at the initial episode. However, residual rates of previously formed coronary aneurysms remain high. Therefore, the importance of carefully managing coronary aneurysms associated with KD remains unchanged.

What is already known on this topic?

- Children with a history of Kawasaki disease (KD) are highly susceptible to disease recurrence (1.5%–4%).
- KD recurrence is a risk factor for developing cardiac sequelae.
- These findings are based on data obtained before high-dose (2 g/kg) intravenous immunoglobulin (IVIG) therapy prevailed in Japan; recent data are needed for re-evaluation.

What this study adds?

- Following high-dose IVIG therapy, KD recurrence is no longer a risk factor for developing cardiac complications, unless cardiac sequelae appear at the initial episode.
- Residual rates of previously formed coronary aneurysms among patients with recurrent KD remain high (approximately 50%).
- Careful management (both prevention and suppression of the progression) of coronary aneurysms associated with KD continues to be of critical importance.

INTRODUCTION

Kawasaki disease (KD) is the leading cause of acquired heart disease among children in developed countries.[1 2] Although its aetiology remains unclear, the recurrence of KD is an interesting clinical feature of the disease. The proportion of recurrent cases among children with a history of KD varies among countries: 3%–4% in Japan,[3–5] 3.8% in Korea,[6] 1.9% in China,[7] 1.5% in Taiwan,[8] 3.5% in Jamaica,[9] 1.7% in the USA[10] and 1.5% in Canada.[11] These figures reflect the genetic predisposition to the disease among races.[12] The incidence rate is the best epidemiological measurement of the frequency of disease occurrence over time.[13] The incidence rate of recurrence among children with a history of KD has remained higher than that of initial occurrence in the general child population in Canada[11] and Japan.[14–16] Moreover, the most important clinical issues associated with KD treatment are the prevention of cardiac sequelae and the suppression of their progression once they have occurred. According to previous studies, patients with recurrent KD were more likely to have cardiac sequelae at the second episode in the USA[10] and Japan,[17] although data from other countries were controversial.[7 11]

Intravenous immunoglobulin (IVIG) therapy is reportedly more effective for reducing cardiac sequelae among patients with KD than aspirin monotherapy.[18 19] In the 1990s, a regimen of 200–400 mg/kg IVIG for five consecutive days was accepted by the Japanese public medical insurance system. Subsequently, a single high-dose IVIG regimen (2 g/kg) was reported to be more effective for KD treatment in the USA.[20] In 2003, a high-dose regimen of 2 g/kg IVIG for 1 day was approved in Japan, and this high-dose IVIG regimen plus aspirin continues to be the standard therapy for KD treatment.

Previous studies[10 17] reporting higher proportions of cardiac sequelae among patients with recurrent KD were mainly based on data obtained before

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2003. In this study, therefore, we aimed to examine the epidemiological features of cardiac sequelae among patients with recurrent KD following the widespread use of high-dose IVIG therapy and to compare these findings with our previous results.

PATIENTS AND METHODS

Study design

Nationwide epidemiological surveys of KD have been retrospectively conducted in Japan every 2 years since 1970. This study was designed to compare two cohorts of patients with recurrent KD. One cohort (previous cohort) was selected from the 11th to 13th nationwide survey databases (1989–1994), while the second (recent cohort) was selected from the 18th to 22nd databases (2003–2012).

Cohort population

In both cohorts, data of the initial and second episodes were linked to follow the chronological changes in cardiac sequelae for each patient. Details of the data linkage method were previously described.[16 17] The following criteria for excluding patients from analyses were adopted in both cohorts: (1) patients who first visited the hospital 15 days after disease onset, (2) patients with recurrence within 2 months (these patients were regarded as recrudescent) and (3) patients with two or more recurrences. Overall, 1842 recurrent patients were selected as the recent cohort from 113 371 KD cases registered in the databases; 559 patients were selected as the previous cohort from 33 976 KD cases, but 300 had missing data related to the types of cardiac sequelae (detailed information on cardiac sequelae was not collected before the 11th nationwide survey). Therefore, after excluding these 300 patients in the previous cohort, 259 patients were eligible for the analyses that required data on the types of cardiac sequelae.

KD diagnosis

Diagnostic guidelines[21] prepared by the Japan Kawasaki Disease Research Committee were adopted for the nationwide surveys: a complete KD case was defined as a patient with at least five of the six principal clinical symptoms; an incomplete KD case was defined as a patient with four symptoms and cardiac lesions or a patient who did not satisfy the diagnostic criteria for complete KD but in whom other diseases were excluded.

Evaluations of cardiac complications

Cardiac sequelae were defined as one of the following findings after 1 month of disease onset: coronary aneurysms including dilatation, coronary stenosis including narrowing, myocardial infarction or valvular lesions. Criteria for coronary aneurysms in KD were defined according to the Japanese Ministry of Health,[22] as follows: an internal lumen diameter of >3 mm in children younger than 5 years, >4 mm in children aged 5 years or older or when the internal diameter of any segment was at least 1.5 times greater than its adjacent segment. A giant coronary aneurysm was defined as an internal lumen diameter of >8 mm. In the recent cohort, data regarding cardiac complications were available in the acute (within 1 month of disease onset) and sequelae phases (1 month after onset); in the previous cohort, the same data were only available in the sequelae phase due to the survey protocol. Patients with coronary aneurysms were categorised into three groups for chronological assessment: (1) patients with giant coronary aneurysms (>8 mm), (2) patients with small or middle-sized coronary aneurysms (3–8 mm) including dilatation and (3) patients without coronary aneurysms.

Table 1 Comparison of the types of cardiac sequelae between the cohorts

	Previous cohort (1989–1994)		Recent cohort (2003–2012)	
	Initial episode	Second episode	Initial episode	Second episode
Total	259		1842	
Without cardiac sequelae, n (%)	231 (89.2)	214 (82.6)	1778 (96.5)	1747 (94.8)
With cardiac sequelae, n (%)	28 (10.8)	45 (17.4)	64 (3.5)	95 (5.2)
Giant coronary aneurysm (>8 mm)	5	4	2	3
+Coronary aneurysm	1	0	0	1
+Coronary stenosis	1	1	0	0
Coronary aneurysm (3–8 mm)	22*	41	57	82†
+Coronary stenosis	0	2	0	1
Coronary stenosis	1*	3‡	0	1§
Valvular lesion	2	0	5	11

Coronary aneurysm includes dilatation; coronary stenosis includes narrowing.
Among these patients, no patients had myocardial infarction.
*One giant coronary aneurysm is included.
†One giant aneurysm is included.
‡One giant aneurysm and two aneurysms are included.
§One aneurysm is included.

Statistical analysis

To calculate the OR with a 95% CI for each variable, unconditional logistic regression models were used. In the models, several factors were included simultaneously to adjust for potential confounding factors. All analyses were carried out using IBM SPSS Statistics software V.25.

RESULTS

Study cohort

The cohort characteristics used for comparison are summarised in online supplementary file 1 (Summary of cohort comparison). Regarding sex and age distribution, no differences were observed. The mean interval between two KD episodes in the previous and recent cohorts was 1.78 and 1.41 years, respectively.

Cardiac sequelae

The types of cardiac sequelae in both cohorts are listed in table 1. In the previous cohort, data for 259 patients with recurrent KD, excluding 300 who were missing information as to the types of cardiac sequelae, were analysed. In the recent cohort, the proportion of recurrent KD patients with cardiac sequelae at the initial and second episodes was 3.5% and 5.2%, respectively. These values markedly decreased compared with those (10.8% and 17.4%, respectively) in the previous cohort. When all data for 559 patients were analysed, these proportions were 12.2% and 19.7%, respectively (see online supplementary file 1). Regarding the types of cardiac sequelae, the recent cohort showed a remarkable decrease in the proportion of coronary aneurysms, regardless of the size of the coronary aneurysms. Although precise comparisons of the stenosis and valvular lesions

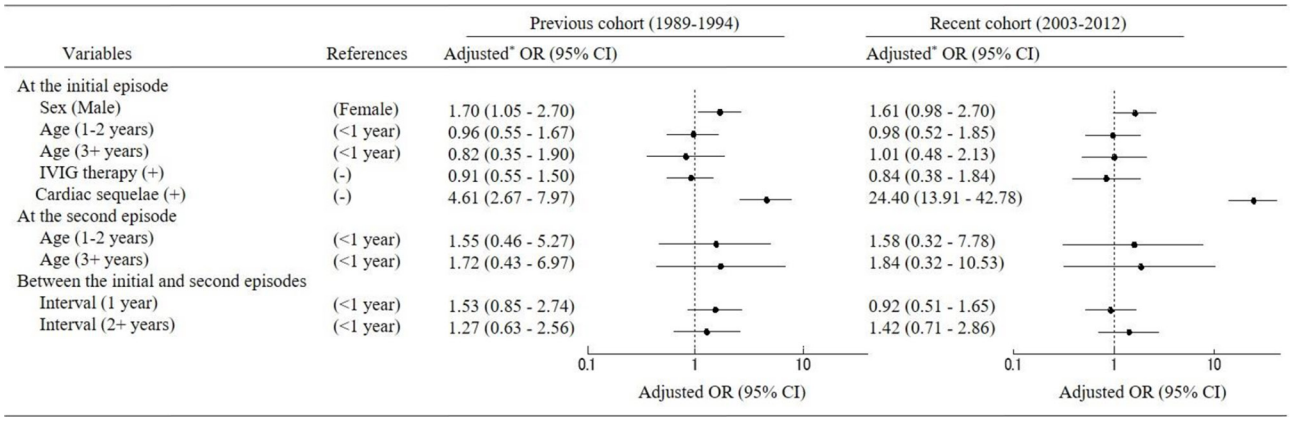

Figure 1 Comparison of the ORs for cardiac sequelae at the second episode between the cohorts. Multivariate analyses were conducted in both cohorts using the same variables for comparison. *Logistic regression models. IVIG, intravenous immunoglobulin.

were difficult because of the small number of cases, a decreased trend in cases with stenosis was observed.

Risk factors for cardiac sequelae development

To compare the two cohorts, multivariate logistic regression analyses for the recent cohort were conducted using the same variables adopted in the previous cohort study (figure 1). Each variable showed a similar trend between the cohorts, except that male sex lost its statistical significance in the recent cohort.

Chronological changes in coronary aneurysms

In the recent cohort, we investigated the chronological changes in coronary aneurysms by linking the data from the initial and second episodes (figure 2). The proportions of coronary aneurysms, including giant aneurysms, at the second episode increased slightly in both phases compared with those at the initial episode. However, when 59 recurrent KD patients with giant coronary aneurysms (n=2) or small or middle-sized aneurysms (n=57) at the initial episode were excluded from analyses, the difference in the proportion of coronary aneurysms between the two episodes disappeared (figure 3). Next, the chronological changes in coronary aneurysms between the initial and second episodes were compared between the cohorts (figure 4). In the recent cohort, the proportions of coronary aneurysms, including giant aneurysms, markedly decreased compared with those in the previous cohort. Conversely, the residual rates of previously formed coronary aneurysms in patients were almost similar between the cohorts. In the previous cohort, two (40%) of five patients with giant coronary aneurysms at the initial episode also had them at the second episode, and 13 (59%) of 22 patients with small or middle-sized aneurysms at the initial episode also had them at the second episode. Similarly, in the recent cohort, one (50%) of two patients with giant coronary aneurysms at the initial episode also had them at the second episode, and 27 (47%) of 57 patients with small or middle-sized aneurysms at the initial episode also had them at the second episode.

DISCUSSION

Research on patients with recurrent KD using nationwide survey databases has two main advantages. First, the chronological changes in cardiac sequelae for the same patients can be followed in a large cohort. Second, in Japan, children with a history of KD have been considered highly susceptible to disease recurrence and more likely to develop cardiac sequelae than the general child population. Thus, the clinical features of this susceptible group, including therapeutic effects, can be determined over time using survey databases.

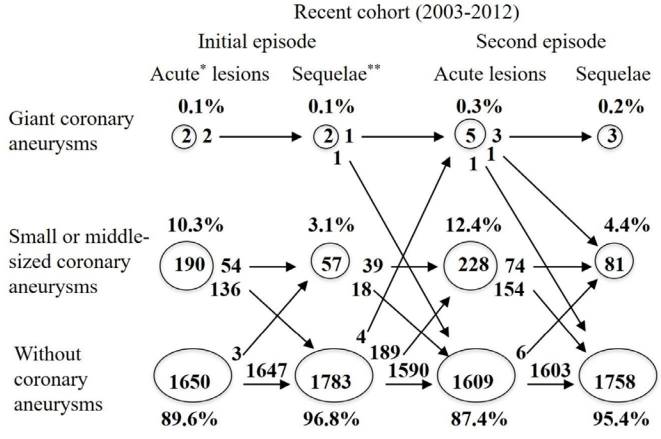

Figure 2 The chronological changes in coronary aneurysms between the initial and second episodes in the recent cohort. Coronary arteries were evaluated in the acute* (within 1 month of disease onset) and sequelae** (1 month after onset) phases.

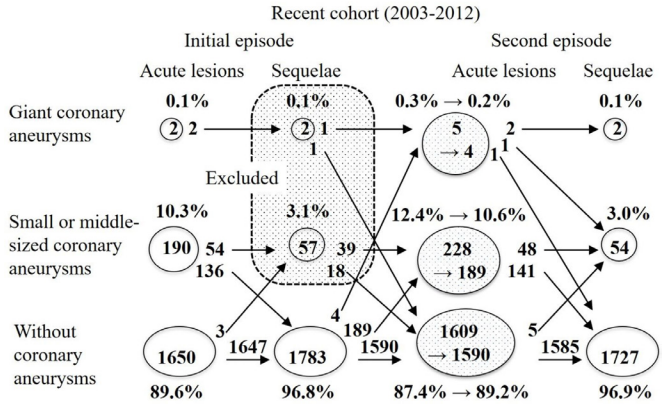

Figure 3 The chronological changes in coronary aneurysms in the recent cohort after 59 patients (shaded area surrounded by dotted line) who had coronary aneurysms in the sequelae phase at the initial episode were excluded from analyses.

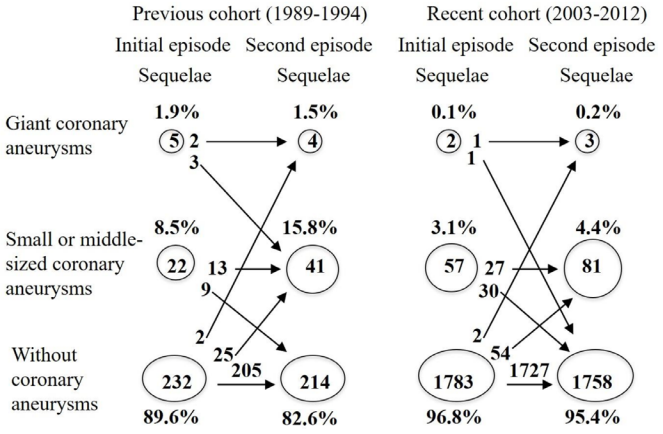

Figure 4 Comparison of the chronological changes in cardiac sequelae between the cohorts.

Comparison of cardiac sequelae

According to data obtained before the widespread use of high-dose IVIG therapy, KD recurrence was associated with an increased risk of developing cardiac sequelae. In the recent cohort, the proportions of recurrent KD patients with cardiac sequelae was significantly decreased compared with those in the previous cohort (table 1). The widespread use of high-dose IVIG therapy likely contributed to this significant clinical outcome.

Comparison of the risk factors for developing cardiac sequelae

Notably, the risk factors for cardiac sequelae at the second episode were almost similar between the cohorts (figure 1). This result suggests that the clinical features of the cardiac sequelae themselves did not change between the cohorts, whereas the proportions of patients who had cardiac sequelae decreased significantly in the recent cohort.

Comparison of the chronological changes in coronary aneurysms

The chronological changes in coronary aneurysms were followed for each patient by data linking (figure 2). The proportions of recurrent KD patients with coronary aneurysms at the second episode slightly increased compared with those at the initial episode. In contrast, the analyses excluding patients with coronary aneurysms at the initial episode showed that the proportions of patients who had coronary aneurysms at the second episode decreased to the same low level as those at the initial episode regardless of the size of the coronary aneurysms (figure 3). Conversely, in the previous cohort, the proportion (15.9%) of recurrent KD patients without cardiac sequelae at the initial episode who developed them at the second episode was higher than the corresponding figure (12.8%) for the overall KD patient population between 1989 and 1994 in Japan (cardiac complications in the acute phase were not examined).[17] It was proposed that repeated assaults due to KD-associated vasculitis might have contributed to increased vulnerability to coronary aneurysms. In the recent cohort, it should also be noted that the proportions of recurrent patients who developed coronary aneurysms in the acute and sequelae phases at the initial episode were 10.4% and 3.2%, respectively, which were almost identical to the corresponding figures (10.0% and 3.2%, respectively) for the overall KD patient population between 2003 and 2012 in Japan. These results suggest that KD recurrence is no longer a risk factor for developing coronary aneurysms mainly due to the widespread use of high-dose IVIG therapy, unless cardiac sequelae appear at the initial episode. Moreover, although the sample sizes were small, studies from China[7] and Canada[11] reported similar trends whereby the KD recurrence was not a risk factor for coronary aneurysms. Given that the Chinese study was conducted from 2002 to 2010, most of the patients with KD had likely received high-dose IVIG therapy. The Canadian study was conducted from 1995 to 2005, although details of the administered dose of IVIG therapy were not described. In the Canadian study, the recurrence rate of KD was approximately half of that reported in Japan. Some studies[23 24] indicated that genetic factors involved in the susceptibility to KD occurrence might affect the severity of cardiac sequelae, which might also have influenced the results of the Canadian study.

Importantly, in both cohorts, approximately half of the coronary aneurysms, including giant aneurysms, regressed or disappeared without progression to a larger size (figure 4). This result was in accordance with previous reports showing that the coronary diameter at 1 month after the onset of KD was an important predictor of late coronary outcomes[25] and that coronary aneurysms properly treated with IVIG therapy, including adjunctive anti-inflammatory medications, were likely to regress.[26] Conversely, approximately half of the coronary aneurysms did not regress despite high-dose IVIG therapy. Therefore, it is strongly recommended that the formation of coronary aneurysms at the initial episode should be prevented by using as intensive treatments as possible in the acute phase to keep patients with KD free of future cardiac sequelae. Furthermore, we conducted the multivariate analysis to investigate the risk factors for developing coronary aneurysms at the second episode among the 1783 patients with recurrent KD who did not possess coronary sequelae at the initial episode (online supplementary file 2). As a result, the existence of acute coronary complications at the initial episode was a significant risk factor for developing coronary aneurysms when they recurred KD. This result complements the aforementioned repeated assault theory regarding the increased vulnerability to coronary aneurysms in patients with recurrent KD and also means that even patients with KD who show transient coronary complications only in the acute phase should be carefully followed up.

Limitations

This study had some limitations. No information on the period between the initial and second episodes was available. Thus, the coronary aneurysm at the initial episode might have disappeared, and a new aneurysm might have appeared and replaced it at the second episode. Moreover, in cases where several coronary aneurysms appeared in one patient, information on the individual aneurysms was not described. Although these possibilities could not be verified in this study, the sample size was sufficiently large to permit reliable analyses. In this study, Z scores were not used for the evaluation of coronary arteries. To follow the size changes of coronary aneurysms, Z scores are more appropriate as they account for the influence of the child's body growth. The fact that many patients (40%–45%) in both cohorts experienced recurrence within 1 year might have minimised this disadvantage.

CONCLUSION

This study suggests that KD recurrence is no longer a risk factor for developing cardiac sequelae in Japan owing to the widespread use of high-dose IVIG therapy, unless cardiac sequelae appear at the initial episode. However, residual rates of previously formed

coronary aneurysms among patients with recurrent KD continue to be high. Thus, the clinical importance of carefully managing coronary aneurysms associated with KD remains unchanged. As the influence of steroid therapy on cardiac sequelae after the RAISE study[27] was not determined in this study, future epidemiological studies are warranted.

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Contributors DS designed the study, conducted the analyses, drafted the initial manuscript and finalised the manuscript. NM enriched the discussions. YN conceptualised the study and supervised the analyses. NM and YN critically reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Nationwide epidemiological surveys of Kawasaki disease have been conducted every 2 years since 1970. All data sets are managed by the Department of Public Health at Jichi Medical University.

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