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ORIGINAL ARTICLE

Coronary artery lesions of incomplete Kawasaki disease: a nationwide survey in Japan

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Abstract Incomplete Kawasaki disease (KD) is associated with delayed diagnosis and treatment, which in turn can lead to the development of coronary artery lesions (CALs). The aim of this study was to determine the epidemiological features of incomplete KD compared with complete KD and to identify risk factors for CALs from incomplete KD patients using data from a nationwide survey of 2007–2008 in Japan. A total of 23,263 patients were classified according to the number of principal clinical signs: 80% (n=18,620) had complete forms of KD, 14.2% had four principal signs, 4.6% had three signs, and 1.2% had only one or two signs. In comparison with complete KD cases, the prevalence of CAL development tended to be larger and the proportion receiving initial intravenous immunoglobulin (IVIG) treatment were significantly smaller in patients with incomplete forms. In addition, hospital attendance after 7 days of illness or later was significantly associated with CAL development in all incomplete groups (OR: 2.52 in total patients with incomplete KD, 3.26 in those with one or two principal signs, 2.94 in those with three signs, 2.35 in those with four signs). *Conclusion* The higher prevalence of CALs in incomplete KD reflects difficulties in diagnosis and delays in treatment. More timely diagnosis and treatment of incomplete KD patients could further prevent the development of cardiac lesions.

Keywords Coronary artery lesion · Diagnosis · Epidemiology · Mucocutaneous lymph node syndrome · Risk factor · Treatment

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Introduction

Kawasaki disease (KD) is an acute febrile vasculitis of unknown cause that typically affects infants and young children. Since it was first reported as "mucocutaneous lymph node syndrome" in 1967 [6, 7], its etiology and pathophysiology have remained unknown and no specific diagnostic laboratory marker has been developed, despite intensive efforts. Therefore, the current diagnosis of KD depends mainly on patients' clinical manifestations according to clinical guidelines in Japan [2] and the United States [11].

One of the most important issues in the treatment of KD is the prevention of cardiac sequelae. Fortunately, the proportion of patients with cardiac sequelae has decreased over time [10], mainly due to progress in KD diagnosis, in identification of coronary artery lesions (CALs) by echocardiography, and in treatments including intravenous immunoglobulin (IVIG) administration. KD remains, however, the leading cause of acquired heart disease among children in developed countries [13, 15]. Therefore, it is crucial to improve existing intensive treatments.

Our recent study found that the percentage of patients with the incomplete form of KD is as high as 15–20% in Japan [9]. Previously, incomplete KD was shown to be

associated with delayed diagnosis and treatment [1, 8, 17], and delayed treatment for KD was also reported to be a risk factor for the development of CALs [3, 19, 21]. Therefore, in order to prevent development of CALs in KD, it is important to recognize differences in clinical risk factors for CALs between the two types of KD and to clinically manage the high risk factors observed in incomplete KD patients. However, a detailed comparison of clinical risk factors has not yet been done. During a 2007–2008 nationwide survey in Japan, we collected data on a number of clinical signs for each KD patient and analyzed their epidemiological features and risk factors for developing CALs according to principal clinical signs.

Materials and methods

Nationwide survey

The 20th nationwide survey of KD was conducted between January 2007 and December 2008 on patients visiting target hospitals in Japan for the treatment of acute KD. Hospitals specializing in pediatrics and hospitals with a pediatric department and 100 or more beds (a total of 2,150 facilities) were requested to participate in the survey. More details of this survey are available in our previous report [10].

Diagnosis of KD

The diagnosis of KD in this study was based on guidelines issued by the Japan Kawasaki Disease Research Committee (5th revision) [2]. Complete KD was defined as having at least five of the following six principal clinical signs: (1) fever persisting for five or more days (inclusive of patients in whom the fever had subsided before the fifth day in response to therapy); (2) bilateral conjunctival congestion; (3) changes to the lips and oral cavity; (4) polymorphous exanthema; (5) changes to peripheral extremities; and (6) acute nonpurulent cervical lymphadenopathy. Although Japanese diagnostic guidelines state that patients with four of the principal clinical signs can be diagnosed as KD when CALs are recognized by two-dimensional echocardiography or coronary angiography [2], in this study, we defined incomplete KD as having four or fewer principal signs, with or without cardiac lesions.

Patients who did not fulfill the Japanese diagnostic guidelines such as those with four principal signs without CALs and those with three or fewer principal signs were reported as having incomplete KD once other diseases had been excluded. Pediatricians used their own judgment based on clinical observations to report such patients with incomplete forms to the nationwide survey; however, we did not collect detailed information about these findings.

Detection of CALs

We observed CALs in KD patients both within 1 month of onset (acute phase) and beyond 1 month after onset (sequelae phase). Almost all patients were assessed for CALs on the basis of two-dimensional echocardiography. In this study, patients with CALs were defined as those having coronary artery dilatation and/or coronary aneurysm and/or giant coronary aneurysm. Criteria for CALs in KD have been defined by the Japanese Ministry of Health [12]; thus, classifying coronary arteries as abnormal if the internal lumen diameter is >3 mm in children younger than 5 years or >4 mm in children 5 years or older, when the internal diameter of any segment is at least 1.5 times greater than an adjacent segment, or when the coronary artery lumen is clearly irregular. A giant coronary aneurysm is defined as an internal lumen diameter >8 mm.

Statistical analysis

We observed the distribution of epidemiological features and the proportion of patients who developed CALs in each group (those with one, two, three, four, and five or six principal signs) as well as in all patients with incomplete forms of KD (those with one to four principal signs). Differences between groups were assessed by analysis of variance with the Dunnett or nonparametric Steel test using the complete KD group (with five or six principal signs) as the reference. Data were expressed as a median (range) or percentages, as appropriate. A two-sided p-value less than 0.05 was considered to be statistically significant. To delineate risk factors, odds ratios (ORs) and their 95% confidence intervals (CIs) for CALs were calculated using multivariate logistic regression analysis to adjust for sex, age, length of illness at first hospital visit, administration of initial IVIG treatment, and administration of steroid therapy. The statistical analysis was performed with SPSS® 13.0 J (SPSS Inc., Chicago, IL) and SAS® 9.2 (SAS Institute Inc., Cary, NC).

This study was approved by the Ethical Board of Jichi Medical University, Shimotsuke, Tochigi, Japan (November 11, 2008, No. 08–39).

Results

Study population

Of the 23,337 KD patients in the 20th nationwide survey, 74 were excluded from this study because data on the number of principal signs were not available. The remaining patients (23,263) were classified according to the number of principal clinical signs: 18,620 had five or six

signs, 3,309 had four, 1,063 had three, 239 had two, and 32 had one. The number of patients with one principal sign was too small for statistical analysis, and clinical features did not differ between patients with two principal signs and those with one. Therefore, these two patient groups were combined for purposes of analysis.

Epidemiological features in complete and incomplete KD patients

No statistical differences were found for the sex ratio, the number of recurrences, or sibling cases among all KD patient groups (Table 1). In contrast, age at onset of KD was significantly lower in patients with incomplete forms of KD than in those with complete cases (median, 17.4 months of age in all incomplete KD vs. 25.1 in complete KD). The proportion of patients experiencing CALs in the acute phase was larger in those with incomplete forms of KD than in complete cases: this difference was significant in patients with one or two principal signs and with four principal signs (15.1% in patients with one or two signs, 14.2% in patients with four signs vs. 8.8% in complete cases). A similar tendency was observed for CALs in the sequelae phase.

Regarding treatment for the disease, the proportion of patients receiving initial IVIG was significantly larger in patients with complete KD than in any of the individual groups with incomplete KD as well as in all patients with incomplete forms (93.2% in complete cases vs. 64.2% in all incomplete KD, 45.0% in patients with one or two principal signs, 51.6% in patients with three signs, and 69.8% in patients with four signs). The day of receiving initial IVIG in patients with incomplete forms was also significantly later than those with complete forms. The proportion of patients receiving additional IVIG or steroids among those with complete forms of KD was also larger than in patients with three or four principal signs and compared with all incomplete KD patients.

Epidemiological features of patients with CALs were then investigated in each group of patients with incomplete forms of KD (Table 2). In the acute phase of the disease, 279 patients were excluded from the population described in Table 1 because they lacked data on the presence or absence of CALs. Similarly, 782 patients were excluded from the analysis of CALs in the sequelae phase. In CALs patients with incomplete forms of KD, age at onset tended to be younger than in CALs patients who fulfilled diagnostic guidelines. In addition, the proportion of CALs patients receiving initial IVIG, additional IVIG, and steroid was significantly larger in complete KD patients than in patients in incomplete groups. Moreover, the time of receiving initial IVIG treatment in each group of incom-

Table 1 Epidemiologic features of patients with Kawasaki disease by the number of principal clinical signs

	No. of principal clinical signs				
	1 or 2 *n*=271 (1.2%)	3 *n*=1,063 (4.6%)	4 *n*=3,309 (14.2%)	1, 2, 3 or 4 *n*=4,643 (20.0%)	5 or 6 *n*=18,620 (80.0%)
Male	156 (57.6%)	622 (58.5%)	1,912 (57.8%)	2,690 (57.9%)	10,791 (58.0%)
Age (months)	11.7 (0.7–167.3)*	15.6 (0.6–178.4)*	18.5 (0.8–216.1)*	17.4 (0.6–216.1)*	25.1 (0.6–237.4)
Day at first hospital visit	3 (1–29)	3 (1–20)	4 (0–30)	4 (0–30)*	4 (0–31)
Recurrences	10 (3.7%)	37 (3.5%)	121 (3.7%)	168 (3.6%)	652 (3.5%)
Sibling cases	1 (0.4%)	21 (2.0%)	39 (1.2%)	61 (1.3%)	265 (1.4%)
Fatal cases	1 (0.4%)*	0 (0%)	0 (0%)	1 (0.02%)	5 (0.03%)
CALs in the acute phase (within 1 month of onset)	41 (15.1%)*	98 (9.2%)	469 (14.2%)*	608 (13.1%)	1,647 (8.8%)
CALs in the sequelae phase (1 month after onset)	20 (7.4%)*	33 (3.1%)	111 (3.4%)*	164 (3.5%)	472 (2.5%)
Initial IVIG treatment	122 (45.0%)*	548 (51.6%)*	2,309 (69.8%)*	2,979 (64.2%)*	17,351 (93.2%)
Day of receiving initial IVIG	6 (1–29)*	6 (1–37)*	5 (1–30)*	5 (1–37)*	5 (1–34)
Additional IVIG administration[a]	14 (11.5%)	59 (10.8%)*	257 (11.1%)*	330 (7.1%)*	3,018 (17.4%)
Steroid therapy	11 (4.1%)	27 (2.5%)*	105 (3.2%)*	143 (3.1%)*	1,074 (5.8%)

Data are presented as number (%) or median (range). Patients who lacked their data on the number of principal signs were exclueded. Multiple comparison with Dunnett or nonparametric Steel test was performed for group comparisons (reference group as one with five or six principal signs vs. other groups

CALs coronary artery lesions, *IVIG* intravenous immunoglobulin

* $P<0.05$ (statistical significance)

[a] Percentage of patients who received additional IVIG among those who received initial IVIG treatment

Table 2 Characteristics of patients with Kawasaki disease who had coronary artery lesions within 1 month of the onset by the number of principal signs

	No. of principal clinical signs				
	1 or 2 *n*=41	3 *n*=98	4 *n*=469	1, 2, 3 or 4 *n*=608	5 or 6 *n*=1,647
Male	25 (61.0%)	68 (69.4%)	317 (67.6%)	410 (67.4%)	1,110 (67.4%)
Age (months)	11.1 (0.9–131.2)	16.6 (2.0–149.6)	18.3 (1.2–176.0)*	17.6 (0.9–176.0)*	27.9 (1.2–200.5)
Day at first hospital visit	4 (1–29)	3 (1–20)	4 (1–30)	4 (1–30)*	4 (1–31)
Initial IVIG treatment	26 (63.4%)*	63 (64.3%)*	389 (82.9%)*	478 (78.6%)*	1,528 (92.8%)
Day of receiving initial IVIG	7 (3–29)*	7 (2–37)*	6 (1–30)*	6 (1–37)*	5 (1–34)
Additional IVIG administration[a]	3 (11.5%)*	11 (17.5%)*	83 (21.3%)*	97 (20.3%)*	643 (42.1%)
Steroid therapy	4 (9.8%)	6 (6.1%)*	32 (6.8%)*	42 (6.9%)*	315 (19.1%)

Data are presented as number (%) or median (range). Patients who lacked their data on the presence or absence of CALs were exclueded. Multiple comparison with Dunnett or nonparametric Steel test was performed for group comparisons (reference group as one with five or six principal signs with CALs vs. other groups with CALs

CALs coronary artery lesions, *IVIG* intravenous immunoglobulin

* $P<0.05$ (statistical significance)

[a] Percentage of patients who received additional IVIG among those who received initial IVIG treatment

plete cases was significantly later than in complete KD cases (median; 6 days from the onset in four principal signs or in all incomplete cases, 7 days from the onset in one or two principal signs or in three signs vs. 5 days from the onset in complete cases). These findings were similar in patients with CALs in the acute phase and in the sequelae phase.

Analysis of potential risk factors for developing CALs

The risk factors for developing CALs were assessed by multivariate analysis (Table 3). In the acute phase of complete KD patients, male sex (OR=1.50, 95% CI=1.35–1.68), ages less than 1 year (OR=1.23, 95% CI=1.08–1.39), ages more than 5 years (OR=1.58, 95% CI=1.36–1.83), visiting hospitals both within 3 days of illness onset (OR=1.24, 95% CI=1.11–1.39) and after 7 days of onset (OR=1.90, 95% CI=1.58–2.29), and administration of steroid therapy (OR=5.11, 95% CI=4.42–5.92) were associated with CAL development. Hospital attendance after at least 7 days of illness was significantly associated with CALs development in all incomplete groups (ORs: 2.52 in all patients with incomplete KD, 3.26 in those with one or two principal signs, 2.94 in those with three signs, 2.35 in those with four signs). Male sex and administration of initial IVIG treatment were also significantly associated with CALs development in patients with incomplete forms, with the exception of those with only one or two principal signs. Hospital attendance at 3 days of illness or earlier and administration of steroid therapy were also significantly associated with CALs development in all incomplete KD patients and in patients with four principal signs. In the sequelae phase, only hospital attendance after at least 7 days of illness was significantly associated with CALs development in incomplete patients, with the exception of those with just one or two principal signs (ORs: 4.65 in all incomplete patients, 4.49 in those with three principal signs, 5.27 in those with four signs; other data not shown).

Discussion

Timely diagnosis of KD is important for the prevention of cardiac lesions. Recommended guidelines for its diagnosis include those from the Japan Kawasaki Disease Research Committee [2] and the American Heart Association [11]. Sonobe et al. reported in 1987 that 6.7% of 675 KD cases were incomplete based on the third revised Japanese guidelines [16], which defined incomplete KD using the same criteria as those used in the present study (the fifth revision). Recent reports of incomplete KD over the past 10 years in Japan suggest a range of 15–20% [10]. Although it is unclear why this figure has increased since Sonobe's report, it is possible that widespread use of diagnostic KD guidelines resulting in more frequent evaluations by echocardiography might have contributed. The diagnostic difficulties of incomplete KD not only hamper its timely diagnosis and treatment but also might lead to a higher incidence rate of CALs. This constitutes one of the most serious problems in the treatment of KD so careful management of clinical risk factors related to CALs in incomplete KD patients is needed for its limitation.

This study showed a higher prevalence of CALs in patients with incomplete presentations of KD compared to those with the complete form based on current Japanese guidelines. This

Table 3 Potential risk factors for developing coronary artery lesion within 1 month of the onset by number of principal signs

	No. of principal clinical signs									
	1 or 2		3		4		1, 2, 3, or 4		5 or 6	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Sex										
Male	1.05 (0.50–2.17)	0.9	1.72 (1.09–2.72)	0.02	1.58 (1.28–1.95)	<0.001	1.56 (1.3–1.88)	<0.001	1.50 (1.35–1.68)	<0.001
Female	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Age (years)										
0	1.44 (0.68–3.07)	0.35	1.15 (0.72–1.82)	0.56	1.03 (0.82–1.29)	0.81	1.06 (0.87–1.28)	0.57	1.23 (1.08–1.39)	0.002
1–4	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥5	3.37 (1–11.35)	0.05	1.30 (0.66–2.56)	0.44	1.20 (0.90–1.61)	0.22	1.26 (0.97–1.63)	0.09	1.58 (1.36–1.83)	<0.001
Day at first hospital visit										
1–3	1.13 (0.49–2.58)	0.78	1.49 (0.92–2.41)	0.11	1.31 (1.05–1.62)	0.02	1.31 (1.09–1.59)	0.005	1.24 (1.11–1.39)	<0.001
4–6	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
≥7	3.26 (1.21–8.76)	0.02	2.94 (1.51–5.71)	0.002	2.35 (1.71–3.24)	<0.001	2.52 (1.92–3.32)	<0.001	1.90 (1.58–2.29)	<0.001
Initial IVIG treatment										
−	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
+	2.05 (0.99–4.26)	0.05	1.62 (1.04–2.54)	0.03	2.22 (1.72–2.87)	<0.001	2.12 (1.72–2.61)	<0.001	0.96 (0.78–1.18)	0.67
Steroid therapy										
−	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
+	2.63 (0.69–10.01)	0.16	2.37 (0.91–6.19)	0.08	2.28 (1.47–3.54)	<0.001	2.34 (1.6–3.41)	<0.001	5.11 (4.42–5.92)	<0.001

Data are presented as odds ratio (*OR*) with 95% confidence intervals (CI)

IVIG intravenous immunoglobulin

might partially reflect the selection bias that incomplete KD patients without CALs are likely to be missed by pediatricians. In the current survey, the percentage of complete KD patients receiving IVIG treatment was more than 90%, which is probably due to widespread use of diagnostic and treatment guidelines on KD. However, the proportions of incomplete KD patients receiving initial IVIG treatment, additional IVIG treatment, or steroid therapy were significantly smaller than in complete KD patients. Similar findings were observed in KD patients with CALs. In addition, the day of receiving initial IVIG treatment in incomplete KD with CALs was significantly later than in those with complete KD with CALs.

Crucially, hospital attendance after seven or more days of illness was shown to be an independent risk factor for developing CALs in all incomplete KD patients regardless of the number of principal clinical signs. This could lead to both delayed diagnosis and later administration of initial IVIG. However, some KD patients with incomplete forms are considered to be of mild severity. Although visiting hospitals at 3 day of illness or earlier, receiving initial IVIG treatment, and receiving steroid therapy were also associated with the development of CALs in some incomplete KD groups, these factors should be considered as markers of disease severity.

Previous studies showed that incomplete clinical manifestations were associated with the development of CALs [5, 14, 17]. However, risk factors for CALs in incomplete KD patients have not been extensively investigated because such patients were only examined if they also had CALs. The present study compared clinical risk factors for CALs in patients with both incomplete and complete presentations of KD and showed that late IVIG administration (≥7 days of illness) was a significant risk factor for the development of CALs in both groups. Considering previous reports that cardiac lesions occurred after a mean of 9.5 days of illness from the onset of KD [4, 18], we propose that treatment of any type of KD should be initiated within 8–9 days of illness onset. To further reduce the likelihood of developing CALs in association with KD, specific laboratory markers would be useful in providing an early diagnosis of KD. However, a previous study showed that both types of KD patients with CALs had similar laboratory measures (C-reactive protein level, white blood cell count, red blood cell count, platelet count, and albumin level) with the exception of serum alanine aminotransferase levels [20]. This is expected to cause difficulties in the identification of a suitable marker.

The present study had some limitations because of its retrospective nature. We did not control the treatment regimens at the various institutions, and we were not able to control the severity of inflammation because we did not collect laboratory data. Furthermore, no data were collected on the precise time at which CALs were observed by echocardiography. Moreover, Japanese diagnostic guidelines do not require echocardiographic evaluation in their diagnosis of incomplete KD, which can result in false-positive cases.

Nevertheless, we believe that the diagnostic reliability of incomplete KD in this survey is high because of the use of additional symptoms and findings, for example, skin changes at the site of the Bacille Calmette–Guérin inoculation.

In conclusion, the higher prevalence of CALs in incomplete KD reflects a diagnostic bias because of the use of echocardiography and difficulties in making the diagnosis leading to treatment delay. More intensive treatments of patients with incomplete presentations, possibly to the same level that is performed in complete KD patients, could lead to the further reduction of CALs.

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