表3　平成17年度 稀少疾患サーベイランス結果

日本小児循環器学会学術委員会　　2006月 9 月 20日

		年齢					性別			生存			家族内発症
	総計	<1	1~6	6~13	13~18	不明	男	女	不明	生存	死亡	不明	家族内有
DCM	56	19	11	10	12	4	35	17	4	41	11	4	5
HCM	53	3	6	22	19	3	31	19	3	48	2	3	17
RCM	11	0	6	3	2	0	9	2	0	11	0	0	2
ミトコンドリア心筋症	11	0	1	6	1	3	3	5	3	7	1	3	0
ARVC	0	0	0	0	0	0	0	0	0	0	0	0	0
LVNC	31	9	9	7	4	2	15	12	4	27	2	2	2
EFE	1	1	0	0	0	0	1	0	0	1	0	0	0
Pompe病	3	2	1	0	0	0	1	2	0	2	1	0	0
急性心筋炎	44	12	9	16	6	1	19	23	2	34	9	1	1
心臓腫瘍	62	30	15	7	4	6	28	26	8	55	1	6	4
原発性肺高血圧症	36	7	5	15	9	0	18	18	0	28	8	0	5
BWG	21	12	4	3	1	1	9	11	1	17	3	1	0
リウマチ熱	6	0	3	1	2	0	3	3	0	6	0	0	0
先天性完全房室ブロック	32	13	5	8	5	1	11	20	1	28	3	1	0
心膜欠損	1	1	0	0	0	0	1	0	0	1	0	0	0
収縮性心膜炎	4	0	1	2	1	0	3	1	0	4	0	0	0
ダウン症の川崎病	1	0	1	0	0	0	1	0	0	1	0	0	0

集計結果（2006年 9 月20日現在）
全配布施設数　　155（評議員在籍施設：118，他施設：37）
回収施設数　　143（評議員在籍施設：113，他施設：30）
回収率　　92%

序

「小児用医薬品承認の新しい流れ —Off-label 薬を安全に正しく使用するために—」

東邦大学医療センター大森病院　小児科，小児科学会薬事委員　佐地　勉

多くの臨床医が最初に遭遇する“腕の見せどころ”が，治療薬の正しい選択と処方であろう。行政側の変革もあって，このところ小児用医薬品への注目度が高まってきている。

それには厚労省研究班の研究課題としても継続されている，①小児医薬品の適正使用，②Off-label 薬の適応承認，③未承認薬の早期承認，④医師主導型治験，⑤小児用臨床評価ガイドラインの確立　　等の領域での進歩が多大な貢献をしてきた。

この研究の源流は，故大西鐘壽先生（前香川医大教授）の功績に依存するところが多く，その後松田一郎班（前熊本大学），そして現在は伊藤進班（香川大学）と受け継がれ，小児用医薬品開発の強力な牽引車として臨床に密接した研究活動が続いている。

この動きの発端となった Epoch Making な公式発表は，平成 11 年 2 月 1 日付け，厚労省からの所謂「104 号通知」（医薬審第 104 号，「適応外使用に基づく承認について」，厚労省健康政策局研究開発振興課長，同医薬安全局審査管理課長　発）であろう。これは，小児の医薬品の適応外使用の承認に関して，「学会から要望があり使用が医療上必要と認められる場合は，充分な科学的根拠（所謂 Evidence）の収集により一部変更承認を考慮する事」という，画期的な通達であった。ちょうどその数日後に班会議があり，会議の席上担当の A 技官がこの通達を配布した時の興奮を今でも鮮明に記憶している。研究班には小児の 20 の分科会の代表が参加し，私の所属する「小児循環器学会」もこの 4 年間に，動脈管開存への PGE 1-CD，川崎病急性期のガンマグロブリン 2 g/kg 超大量投与，同アスピリン療法，2 歳以下の先天性心疾患有症状例への抗 RSV 抗体シナジスの適応が，円滑な過程を経て承認された。

一方，薬価算定委員の小児専門委員として参加しているこの 6 年間でも，多くの小児用医薬品が適切な価格で承認されてきていることは，厚労省—医薬品審査機構—小児科医—そして研究班の連携がうまくとられてきた証拠といえるのではないか。また，小児用医薬品の薬価算定方式や，所謂開発に対する“インセンティブ”にも変化が見られてきたことは好ましい。

今後も小児用医薬品の開発については，1999 年 FDA から提出された ICH-E 11（小児用ガイダンス），新 GCP の遵守，適切な IRB の運営，正しい臨床試験の計画立案が必要であると考える。そして最後にやはり，若い小児科医の臨床薬理学に対する理解と興味，さらに小児用医薬品の承認申請に積極的に参加するという姿勢が求められる時代となってきているのではないか。本特集は日常診療における安全で有用な“子どもへの投薬”について，その領域の Experts に執筆をお願いした。日常の診療または今後の研究の一助になれば幸いである。

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Original Article

Prevalence of coronary artery abnormality in incomplete Kawasaki disease

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Abstract

Background: The aim of the present study was to determine the prevalence of coronary artery abnormality (CAA) and other clinical features in patients with incomplete Kawasaki disease (iKD) using the data from the 17th Japanese nationwide survey of KD.

Methods: iKD was defined as the presence of four or fewer of the principal symptoms of the Japanese diagnostic guidelines, regardless of whether the patient had CAA. A total of 15 857 cases were analyzed.

Results: Among 15 857 cases, 83.9% of patients had five to six principal symptoms (complete KD: cKD), and 16.1% had iKD. The prevalence of CAA in cKD was 14.2%, and 18.4% in iKD. The prevalence of CAA in patients with four principal symptoms was 18.1%, which was higher than in cKD cases (14.2%). Although the reliability of the data has some limitations, the prevalence of CAA among patients with one to three symptoms was 19.3%. Among all CAA patients, 14% had four symptoms, and 6% had only one to three symptoms.

Conclusion: Incomplete KD should not be equated with mild KD. Patients with four principal symptoms were comparable to cKD with respect to CAA occurrence. In patients with one to three symptoms also, especially in those under 1 year and older than 4 years of age, other significant symptoms and laboratory findings of the guidelines are very important in making a correct and early diagnosis of iKD so as to prevent CAA.

Key words coronary artery abnormality, epid emiologic survey, incomplete Kawasaki disease, Kawasaki disease.

The etiology of Kawasaki disease (KD) is still unknown even though 38 years have passed since the first report by Kawasaki.[1,2] The diagnosis of KD is made clinically using the diagnostic guidelines for KD.[3–6] The latest fifth revised Japanese KD guidelines[4] are shown in Table 1. In practice, many patients have incomplete (atypical) Kawasaki disease (iKD) because they do not fulfill the diagnostic criteria. Some of the patients with iKD develop coronary artery abnormality (CAA).[7–16] There is growing concern regarding iKD and there has been a lack of data and analysis of any large series of iKD patients. We analyzed the prevalence of CAA in iKD patients using the data from the nationwide survey of KD in Japan conducted in 2003.[17] In this report we have defined iKD as the presence of four or fewer of the principal symptoms (principal clinical findings) of KD according to the Japanese guidelines, regardless of the presence or absence of CAA. In the Japanese guidelines fever is not an essential criterion, and the size of enlarged cervical lymph node is not included as a criterion. We determined the prevalence of CAA in iKD patients, the relationship between the number of principal symptoms and the prevalence of CAA, as well as other clinical features of iKD.

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Methods

We analyzed the data from the 17th Japanese nationwide survey of KD conducted in 2003. The 2003 survey collected cases from 2001 to 2002.[17] Nationwide surveys, which have collected data on approximately 90% of all cases in Japan, have been conducted every 2 years since 1970. The precise method used in the nationwide KD surveys has been previously described.[18,19]

The major information included in the questionnaire were age, gender, date of onset, clinical classification of KD as made by the reporting doctors, the presence of CAA in the

Table 1 Fifth revised Japanese KD guidelines[4]

Diagnostic Guidelines for Kawasaki Disease
(MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome)
(The 5th Revised Edition, February 2002)
This is a disease of unknown etiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories: principal symptoms and other significant symptoms or findings.

A. Principal symptoms

1. Fever persisting ≥5 days (inclusive of patients in whom the fever has subsided before the fifth day in response to therapy)
2. Bilateral conjunctival congestion
3. Changes of lips and oral cavity: Reddening of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
4. Polymorphous exanthema
5. Changes of peripheral extremities: (initial stage) reddening of palms and soles, indurative edema (convalescent stage) membranous desquamation from fingertips
6. Acute non-purulent cervical lymphadenopathy

At least five items of 1–6 should be satisfied for diagnosis of Kawasaki disease. However, patients with four items of the principal symptoms can be diagnosed with Kawasaki disease when coronary aneurysm or dilatation is recognized by 2-D echocardiography or coronary angiography.

B. Other significant symptoms or findings

The following symptoms and findings should be considered in the clinical evaluation of suspected patients.

1. Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR/QT intervals, abnormal Q wave, low-voltage QRS complexes, ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly), 2-D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (axillary etc.), angina pectoris or myocardial infarction
2. Gastrointestinal tract: Diarrhea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase of serum transaminase
3. Blood: Leukocytosis with shift to the left, thrombocytosis, increased ESR, positive CRP, hypoalbuminemia, increased α2-globulin, slight decrease in erythrocyte and hemoglobin levels
4. Urine: Proteinuria, increase of leukocytes in urine sediment
5. Skin: Redness and crust at the site of bacille Calmette–Guérin inoculation, small pustules, transverse furrows of the finger nails
6. Respiratory: Cough, rhinorrhea, abdominal shadow on chest X-ray
7. Joint: Pain, swelling
8. Neurological: CSF pleocytosis, convulsion, unconsciousness, facial palsy, paralysis of the extremities

REMARKS

1. For item 5 under principal symptoms, the convalescent stage is considered important.
2. Non-purulent cervical lymphadenopathy is less frequently encountered (approx. 65%) than other principal symptoms during the acute phase.
3. Male : Female ratio, 1.3–1.5:1; patients under 5 years of age, 80–85%; fatality rate, 0.1%.
4. Recurrence rate: 2–3%; proportion of siblings cases: 1–2%
5. Approximately 10% of the total cases do not fulfill five of the six principal symptoms, in which other diseases can be excluded and Kawasaki disease is suspected. In some of these patients, coronary artery aneurysm (including so-called coronary artery ectasia) have been confirmed.

CRP, C-reactive protein; CSF, cerebrospinal fluid; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate.

acute phase (the most severe lesion in the acute phase) and the sequela phase (after the 29th day of illness), the presence of each of the six principal symptoms, and the mode of treatment.

The diagnostic classification of KD as used in epidemiologic surveys in Japan consists of definitive KD-A (dKD-A), definitive KD-B (dKD-B), and suspected KD (sKD). Definitive KD-A is the presence of five or six principal symptoms. Definitive KD-B is the presence of four symptoms and CAA. Suspected KD is that which does not fulfill the guideline criteria, but is nevertheless suspected of being KD. Suspected KD includes the presence of four symptoms without CAA and the presence of one to three symptoms without regard to CAA. Based on the presence definition, cKD is identical to dKD-A, and iKD includes both dKD-B and sKD (Table 2).

The classification of CAA was based on that made by the reporting doctors. The common classification of CAA in patients under 5–6 years of age is: normal (N, no dilating lesion); small aneurysm or ectasia (An-S, maximum diameter of coronary aneurysm <4 mm); medium aneurysm (An-M, diameter 4–7.9 mm); and large (giant) aneurysm (An-L, diameter ≥8 mm).

The 17th nationwide survey questionnaire was sent to 2413 hospitals that have more than 100 beds and a pediatric department; 68% of the hospitals responded. A total of 16 925 cases from 2001 through 2002 were reported.[17] From them we selected 15 857 patients whose questionnaires did not contain overlapping or incomplete answers.

For the purposes of analysis, we rearranged the diagnostic groups based on the reported number of principal symptoms and the presence of CAA.

Table 2 Official and present classification of Kawasaki disease

No. principal symptoms	CAA (acute phase)	Official Japanese epidemiologic classification	Present classification
5–6	–/+	Definitive KD-A (dKD-A)	Complete KD (cKD)
4	+	Definitive KD-B (dKD-B)	Incomplete KD (iKD)
4	–	Suspected KD (sKD)	Incomplete KD (iKD)
1–3	–/+	Suspected KD (sKD)	Incomplete KD (iKD)

CAA, coronary artery abnormality; KD, Kawasaki disease.

The variables studied were: (i) the prevalence of diagnostic groups, the male to female ratio, and the percentage who received i.v. immunoglobulin (IVIG) treatment in each group; (ii) the prevalence of each of the six principal symptoms in iKD and cKD; (iii) the age distribution and the prevalence of CAA and the percentage of iKD in each age group; (iv) the prevalence of CAA in the acute phase and the sequela phase; (v) the relationship between the number of principal symptoms and the prevalence of CAA; and (vi) the number of principal symptoms for each CAA patient.

Results

Of the 15 857 patients, 9092 were male and 6765 were female. The male to female ratio was 1.31:1.

The number of patients and the percentages of the different diagnostic groups were: (i) dKD-A (cKD), $n = 13\,301$ (83.9%); (ii) dKD-B, $n = 339$ (2.1%); and (iii) sKD, $n = 2217$ (14.0%). Therefore, the percentage of cKD was 83.9%, and that of iKD was 16.1%.

The male : female ratio in each diagnostic group was: (i) dKD-A (cKD), 1.35:1; (ii) dKD-B, 1.80:1; (iii) sKD, 1.25:1; and (iv) iKD, 1.31:1.

The percentage of patients receiving IVIG treatment (regardless of the mode of treatment) in each group was: (i) dKD-A (cKD), 92.4%; (ii) dKD-B, 78.2%; (iii) sKD, 59.0%; and (iv) iKD, 61.6%.

The prevalence of each individual principal symptom in both the cKD and iKD groups is shown in Table 3. The prevalence of cervical lymphadenopathy and extremity changes became lower in the iKD group. The percentage of cases of fever duration <5 days was 1.2% in cKD and 19.7% in iKD.

Table 3 Prevalence of principal symptoms in cKD and iKD

Principal symptoms	cKD (%)	iKD (%)
1. Fever persisting 5 days or more	98.8	80.3
2. Conjunctival congestion	96.9	75.6
3. Changes in lips and oral cavity	95.7	62.8
4. Rash	94.0	64.9
5. Changes in extremities	90.8	44.3
6. Cervical lymphadenopathy	75.3	38.6

cKD, complete Kawasaki disease; iKD, incomplete Kawasaki disease.

The age groups with a high proportion of iKD were under 1 year of age and ≥5 years of age. The age groups with a high prevalence of CAA were below 6 months of age and ≥5 years of age, as shown in Table 4.

The CAA prevalence of iKD was higher than that of cKD in both acute and sequelae phases. Details are shown in Table 5.

The number of principal symptoms correlated inversely to the prevalence of CAA as shown in Table 6.

The number of principal symptoms among all CAA patients was: (i) 5–6 symptoms, 80%; (ii) 4 symptoms, 14%; and (iii) 1–3 symptoms, 6%.

Discussion

The diagnosis of KD is made clinically using the KD diagnostic guidelines. However, the definition of iKD has not yet been established. In Japan, a case is classified as sKD when the patient does not fulfill the diagnostic criteria, but the diagnosis of KD is highly likely after excluding known mimicking diseases. The number of sKD cases has been included in the total number of KD cases reported in the nationwide surveys. Generally speaking, sKD appears to be identical to iKD. However the definitions of cKD, sKD and iKD differ depending upon which guidelines have been used. The Japanese guidelines have been revised five times,[3] and they include two major revisions. Since the first guideline, fever (≥5 days) has not been an essential criterion. In the first guideline published in 1970, cervical lymphadenopathy was not included in the five principal symptoms. In the second revised guidelines published in 1974, the presence of cervical lymphadenopathy, with no reference to size, was added to the list of principal symptoms. With the high availability of echocardiography in Japan, the fourth revised guidelines, published in 1984, defined the presence of four principal symptoms and CAA, confirmed by either angiography or echocardiography, as definitive KD-B (dKD-B). From an international viewpoint there are significant differences between the Japanese and the US guidelines. The US guidelines include fever persisting at least 5 days as an essential criterion, and they define the size of cervical lymph node as ≥1.5 cm.[5,6]

Table 4 Proportion of iKD and prevalence of CAA in the acute phase by age group

Age group	Proportion of iKD (%)	CAA in cKD + iKD (%)	CAA in cKD (%)	CAA in iKD (%)
1. ≤5 months (9.6%)	24.1	19.1	17.4	24.3
2. 6–11 months (16.0%)	20.4	14.8	13.6	19.3
3. 1 and 2 years (41.5%)	14.2	13.2	12.8	15.6
4. 3 and 4 years (21.3%)	12.5	15.0	14.9	15.7
5. ≥5 years (11.6%)	17.2	18.5	17.2	23.1

CAA, coronary artery abnormality; cKD, complete Kawasaki disease; iKD, incomplete Kawasaki disease.

Table 5 Prevalence of CAA in the acute phase and in the sequela phase by diagnostic group

Diagnostic group	*n*	An-S (%)	An-M (%)	An-L (%)	Total (%)
Acute phase					
cKD (dKD-A)	13 301	12.2	1.8	0.2	14.2
iKD (dKD-B + sKD)	2556	15.7	2.5	0.2	18.4
(dKD-B)	(339)	(88.2)	(10.3)	(0.6)	(99.1†)
(sKD)	(2217)	(4.6)	(1.3)	(0.1)	(6.0)
Total	15 857	12.8	1.9	0.2	14.9
Sequelae phase					
cKD (dKD-A)	13 301	2.9	1.2	0.3	4.4
iKD (dKD-B + sKD)	2556	3.8	1.9	0.2	5.9
(dKD-B)†	(339)	(19.2)	(0.7)	(0.6)	(27.5)
(sKD)	(2217)	(1.4)	(1.0)	(0.1)	(2.5)
Total	15 857	3.0	1.3	0.3	4.6

†Three patients had no CAA in the acute phase but An-S in the sequelae phase. An-L, large aneurysm; An-M, medium aneurysm; An-S, small aneurysm; CAA, coronary artery abnormality; cKD, complete Kawasaki disease; dKD-A, definitive Kawasaki disease-A; dKD-B, definitive Kawasaki disease-B; iKD, incomplete Kawasaki disease; sKD, suspected Kawasaki disease.

It is very important to note that the diagnosis of dKD-B cannot be made clinically without echocardiography. Moreover, many case reports of incomplete (atypical) cases have used different guidelines.[7–16] Given this, we defined iKD as the presence of fewer than five principal symptoms, without regard to the presence or absence of CAA; this is the same definition as that used in the third revised Japanese guidelines. According to this definition, iKD encompasses dKD-B and sKD. cKD is classified as the presence of more than four symptoms (Table 2).

We found the prevalence of iKD to be 16.1% in the present study. There appears to have been a recent increase in the percentage of iKD. In 1987 Sonobe and Kawasaki reported that only 6.7% of 675 cases were iKD using the same definition.[7] An increase in the percentage of iKD has also been noted in the two previous Japanese nationwide surveys.[20–22] The 15th survey reported 12 966 KD cases from 1997 through 1998; based on the classification given by the reporting doctors, the percentage of iKD was 15.7%. The 16th survey reported 15 314 KD cases from 1999 through 2000, and the percentage of iKD was 17.9%. The true reason for this increase remains an enigma.

The male : female ratio in cKD and iKD was essentially the same. The male : female ratio was high in the dKD-B group because every dKD-B case must, by definition, included CAA, and CAA is more common in male subjects.[18,23]

In the present study the total proportion of those receiving IVIG treatment was 87.5%. It is worth noting that IVIG treatment in Japan and in the USA is different. In Japan, IVIG is not indicated in all cases of KD, but only in severe cases; the IVIG dose ranges from 1–2 g/kg, with treatment duration ranging from 1 to 5 consecutive days. Therefore the prevalence of CCA in Japan might have been different if US therapy had been utilized.

The percentage of patients receiving IVIG treatment was lower in iKD (61.6%) than in cKD (92.4%). We suppose that one important reason for this findings is the difficulty of making correct and/or early diagnosis of iKD, especially of dKD-B. The percentage of patients receiving IVIG treatment was the lowest in sKD (59.0%) probably due to diagnostic problems as mentioned before and the lower prevalence of CAA in sKD (6.0%) compared to that of cKD (14.2%). Fukushige *et al.* also reported that the prevalence of CAA in sKD was 4% of 25 cases.[10] The most likely reason for this is that patients with four principal symptoms and CAA were not included in the sKD group, and the patients with four principal symptoms and no CAA comprised approximately 70% of the sKD case group.

In regard to the six principal symptoms, in the present study the prevalence of lymphadenopathy and changes in the extremities decreased markedly in iKD as compared with cKD. As in previous reports, the least-seen principal symptoms in iKD

Table 6 Prevalence of CAA in the acute phase by the number of principal symptoms

No. principal symptoms (%)	An-S (%)	An-M (%)	An-L (%)	CAA total (%)
1 (0.1)	12.5	12.5	0.0	25.0
2 (0.8)	17.6	5.6	0.0	23.2
3 (3.5)	14.1	3.4	0.5	18.0
4 (11.7)	16.1	1.9	0.1	18.1
5 (40.7)	11.2	1.5	0.2	12.9
6 (43.1)	13.1	2.0	0.3	15.5
Total (100)	12.8	1.9	0.2	14.9

An-L, large aneurysm; An-M, medium aneurysm; An-S, small aneurysm; CAA, coronary artery abnormality.

were lymphadenopathy followed by changes in the extremities or rash.[7,10–12] Of note, 1.2% of cKD patients and 19.7% of iKD patients did not satisfy the fever criterion.

The age groups with a high proportion of iKD were those of under 1 year and ≥5 years. The age groups with a high prevalence of CAA were those of below 6 months of age and ≥5 years. These findings support the existence of age as a risk factor for CAA.[14,24,25] Thus, in these at-risk age groups, when KD is suspected, one must be aware of iKD and try to make an accurate diagnosis.

The prevalence of CAA was higher in iKD (18.4%) than in cKD (14.2%). A high prevalence of CAA in iKD was also noted in the two previous (15th and 16th) nationwide surveys.[20–22] In the 15th survey (12 966 patients) the prevalence of acute phase CAA in iKD patients was 20.7%, and 19.0% in cKD patients. In the 16th survey (15 314 patients), the prevalence of acute-phase CAA in iKD patients was 18.6%, and 16.9% in cKD patients. Thus, the high prevalence of acute-phase CAA in iKD has been demonstrated in surveys involving a large number of cases.

The relationship between the number of principal symptoms and the prevalence of CAA is a very important in learning more about iKD. The purpose of the present study was to analyze this relationship. The 17th survey was the first survey to collect data on the presence of the six principal symptoms in all cases. The prevalence of CAA in patients with four principal symptoms (18.4%) was higher than in patients with five to six symptoms (14.2%). Moreover there was a trend for the prevalence of CAA to increase as the number of symptoms decreased. The observed trend was contrary to the initial clinical expectations, especially in patients with fewer than four symptoms. There are several probable explanations for this finding. If a pediatrician suspected that a patient had iKD, the likelihood of reporting the case to the nationwide survey probably increased when the patient had CAA. In contrast, when a patient did not develop CAA, the likelihood of making the diagnosis of iKD and reporting the case to the survey probably decreased. We therefore suspect that there were many unreported cases of iKD involving patients with one to three symptoms and without CAA. We surmise that had these cases been reported, the prevalence of CAA among patients with one to three principal symptoms would be lower. Therefore, determining the true prevalence of CAA in iKD based on a nationwide survey is very difficult. Nevertheless, this survey did illustrate that there are many iKD patients with one to three symptoms and CAA including large aneurysms.

With respect to patients with four principal symptoms, although we consider the reliability of the reported number of cases to be high, there may be a small number of unreported cases of patients without CAA. If this is true, the true prevalence of CAA would be lower, close to that of cKD. It is very important that patients with four principal symptoms should be regarded as comparable to patients with five to six symptoms (cKD) in regard to CAA prevalence. Echocardiography and other studies that help diagnose KD are indispensable in patients with four principal symptoms regardless of whether the fever criterion is met.

We feel that the reliability of the diagnosis of iKD in this survey is high for three reasons. First, other significant symptoms or findings (other significant clinical and laboratory findings) of the guidelines are very important in making the diagnosis of KD, especially iKD. In Japan, all children receive a bacille Calmette–Guérin (BCG) vaccine, and it is widely recognized that unusual skin changes such as redness and crust appear at the BCG site when children have KD. Skin changes are very helpful in making an early diagnosis of KD, including iKD. The second reason is that most Japanese pediatricians, both practitioners and hospital staff, are very experienced in making the diagnosis of KD, including iKD, due to the high incidence of KD in Japan. The third is the high availability of echocardiography in Japan. All patients in this survey had echocardiograph evaluation.

An analysis of the number of principal KD symptoms among all CAA patients found that 6% had only one to three principal symptoms while 14% had four symptoms. In total, 20% of the CAA occurred in iKD patients.

Thus, iKD is very important from the point of view of CAA. The incidence of iKD has increased along with the incidence of cKD. Strict adherence to current guidelines, which are directed primarily to cKD, may increase the risk of a missed or delayed diagnosis of iKD, and thereby lead to the development of CAA.[11]

The first KD guidelines were developed to establish the etiology, epidemiology, and clinical aspects of a new and unfamiliar disease. Therefore initial guidelines were very strict in order to exclude KD-mimicking diseases. Since then a large amount of knowledge and data on KD, including that in the present report, have accumulated. New unified world KD guidelines, appropriate for both epidemiologic and clinical use, are needed to avoid confusion and to provide updated guidance.

The present study has some limitations. As in any mass survey, there may be some incorrect reports. With respect to the reliability of the diagnosis of iKD, with the exception of echocardiography, other significant symptoms or findings were not surveyed. However, as discussed before, we believe that the reliability of the diagnosis of iKD was high.

Regarding the prevalence of CAA in each diagnostic group, the result is obtained not from a randomized control trial but from the epidemiologic survey. There are many factors as to the prevalence of CAA: the illness day of diagnosis, the illness day of starting IVIG treatment, the mode of IVIG treatment, an existence of prejudice that incomplete cases are milder compared to complete cases, and the estimated number of unreported cases to the survey. Thus simple comparison of the prevalence between diagnostic groups may not be appropriate. However we believe that the comparison of the prevalence of CAA between cKD and iKD in the present study has significant practical meaning.

In conclusion, iKD, defined as the presence of fewer than five principal symptoms in the Japanese guidelines, had a high prevalence of CAA when compared with cKD. In particular, the prevalence of CAA in patients with four principal symptoms was equal to or higher than that of cKD. iKD patients with four principal symptoms definitively require echocardiography and blood examinations in the guidelines to make a diagnosis of KD more accurately.

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Utility of Coronary MR Angiography in Children with Kawasaki Disease

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OBJECTIVE. Although coronary arterial lesions due to Kawasaki disease (KD) should be evaluated as early as possible after the acute phase, conventional X-ray coronary angiography poses high risks for young children with the disease. The use of noninvasive MR coronary angiography is desirable, although it is difficult to produce clear images in young children. We developed a method to improve the quality of MR coronary angiography in young children. MR coronary angiography with vector electrocardiogram gating, real-time navigator-echo, 3D, steady-state free precession was performed in 35 children with KD. Many parameters (i.e., field of view, acquisition delay, turbo-field echo-factor, navigator window, and resolution) were optimized for each patient.

CONCLUSION. Optimization resulted in the acquisition of high-resolution and high-signal images of the coronary arteries. It remarkably improved not only the quality of the images, but also the detection rate of coronary artery segments. MR coronary angiography is a useful method for evaluating coronary aneurysms from the early stages of KD, even in infants and small children.

Keywords: coronary aneurysm, Kawasaki disease, MR coronary angiography, pediatric imaging, whole-heart imaging

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Coronary aneurysms due to Kawasaki disease (KD) decrease in size soon after the acute phase, which is defined as the first 30 days of illness. Evaluation of aneurysmal size is necessary for risk stratification and therapeutic management as soon as possible after the acute phase. Furthermore, aneurysms often progress to obstructive lesions in the late stage of KD [1]. Therefore, patients with aneurysms after KD need follow-up with coronary angiography (CAG) throughout their lives.

Most patients with KD are infants and children younger than 4 years [2], and CAG often entails risk for such young children. The risks include worsening of the anemia of KD due to bleeding from a punctured femoral artery; thrombotic occlusion of the femoral artery due to puncture of a postinflammatory vessel in the hypercoagulable state, which continues more than 1 year after KD [3]; and myocardial infarction, which sometimes occurs during or after CAG. The considerable radiation exposure of frequent CAG also is a serious problem for young children. These risks indicate the need for a noninvasive simple method of evaluating coronary aneurysms.

Although the usefulness of MR CAG in adults is well known [4, 5], the effectiveness of this technique in infants is not well established. Moreover, to our knowledge, there have been no reports of MR CAG performed on infants. The procedure is difficult because infants have a narrow coronary artery (1–2 mm in diameter) and a fast heart rate (80–130 beats/min) and cannot hold their breath during the examination. However, the development of a new respiratory gating technique (navigator echo) [6] whereby MR CAG can be performed with the patient breathing freely has led to the possibility of visualizing the coronary arteries of infants. We studied the utility of MR CAG in visualizing coronary arterial lesions in patients younger than 6 years with KD. We used cardiac gating and real-time navigator echo technique with radial k-space sampling and a 3D steady-state free precession (SSFP) MRI sequence [7–9].

Materials and Methods

Patients

This retrospective study included 35 patients younger than 6 years who underwent MR CAG between September 2003 and December 2004. These children were undergoing follow-up because a transient dilated lesion had been found during the acute phase of KD or coronary arterial lesions had been found as sequelae of KD. The patients were 10 girls

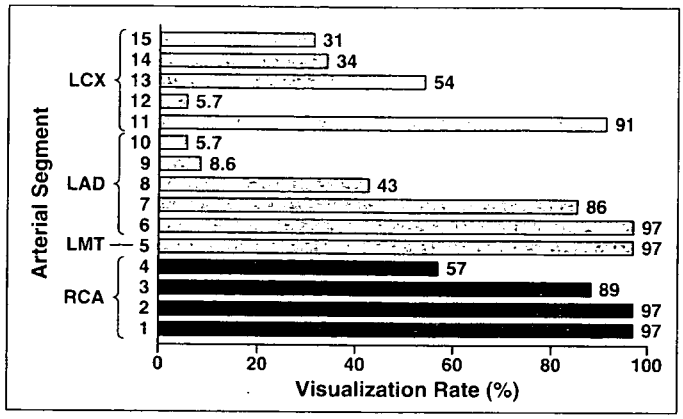

Fig. 1—Graph shows rate of visualization of each segment of coronary artery (n = 35). LCX = left circumflex branch, LAD = left anterior descending branch, LMT = left main trunk, RCA = right coronary artery.

and 25 boys with an age range of 8 months to 6 years 7 months (median age, 3 years 7 months). The heart rate range was 70–127 beats per minute (BPM) (mean ± SD, 103 ± 14 BPM), and the body weight range was 5.6–22.6 kg (mean weight, 12.9 ± 4 kg).

All patients were given sodium trichloroethylene phosphate syrup (0.8–1.0 mL/kg) so that they could sleep during the imaging examination. If the syrup was not effective, we administered thiopental sodium (2–5 mg/kg) by IV infusion. The interval between MR CAG and cardiac sonography for the 35 patients was 0–90 days (median, 6 days). Five patients had undergone CAG follow-up, and the interval between CAG and MR CAG was 5–240 days (median, 60 days). Written informed consent was obtained from the parents of all participants before each MR CAG examination. The study was approved by the committee on clinical investigations at our hospital.

Imaging

All studies were performed with a 1.5-T whole-body fast-gradient (maximum gradient, 30 mT/m; maximum slew rate, 150 mT/m/ms) MRI system (Gyroscan Intera Master Gradient, Philips Medical Systems) equipped with cardiac software. Because of the small body size of infants, a two-element flex-medium coil (Flex-M, Philips Medical Systems) was used instead of a five-element synergy cardiac coil for signal reception. The Flex-M coil is a set of two oval receiver coils with an external diameter of 170 × 200 mm. One coil was set on the chest and the other on the back [10].

Three-dimensional SSFP with vectorcardiographic real-time navigator echo technique was used to visualize the coronary arteries without contrast material. Two methods were used for slice positioning. Three-point-plan scanning [11] was used for 20 patients, and whole-heart imaging [12] was used for 15 patients. The images were reconstructed into maximum-intensity-projection, curved multiplanar reformation, soap-bubble maximum-intensity-projection (Philips Medical Systems), and volume-rendered (M900 Quadra system, Ziosoft) images. For three-point-plan scanning and whole-heart imaging, the diastolic rest period was defined through identification of the heart movement of each patient with 2D SSFP retrospective cine MRI with vectorcardiography. Classification of the coronary arteries into American Heart Association segments [13] increased the visualization rate. The targeted segments evaluated were the right coronary artery (segments 1–4), left main trunk (segment 5), left anterior descending branch (segments 6–10), and the left circumflex branch (segments 11–15).

Three-point-plan scanning and whole-heart imaging—Navigator gating with prospective slice correction was used to compensate for respiratory motion. A flow-insensitive T2-weighted preparatory pulse [14] for contrast enhancement without the use of contrast material was followed by a localized anterior saturation preparatory pulse, navigator echo, a spectrally selective fat-saturation pulse (spectral presaturation by inversion recovery), and a 3D segmented k-space gradient-echo sequence (TR range/TE range, 4.3–5.0/2.2–2.5; flip angle range, 90–100°; radial k-space sampling technique). These sequences were followed by three-point-plan scanning and whole-heart imaging with eight phase-encoding steps per cardiac cycle, so-called bright-blood imaging. Data were acquired along the major axis of the artery. Flow-compensating gradients were not used. Slices 1.8 mm thick (interpolated to 0.6 mm) were acquired with a 180- to 200-mm field of view and were reconstructed with a 512 × 360 matrix (in-plane voxel size, 0.35 × 0.35 mm). The parallel imaging technique of sensitivity encoding [15] was used, usually with accelerator factors 1.3 in the phase direction and 1.0 in the slice direction.

Cine MRI—An ECG-triggered turbo field-echo SSFP cine MRI sequence (one signal acquired per R-R interval; heart rate phase, 80; cardiac synchronization, retrospective gating) was applied in the transverse plane at the level of the proximal to medial right coronary artery for visual determination of the optimal diastolic rest period. The sequence parameters were as follows: 4.2/1.88; flip angle, 60°; field of view, 220 mm. A 192 × 154 matrix with cartesian k-space sampling yielded an in-plane resolution of approximately 1.15 × 0.87 mm (reconstructed 256 × 256 matrix, 0.8 × 0.8 mm).

Slice positioning technique: three-point-plan scanning, whole-heart imaging, and cine MRI—For three-point-plan scanning, the axial image was used to determine the imaging plane for one targeted artery. Three points were plotted on the targeted artery, and the computer was used to calculate the position of the scanning plane. Twenty to 30 slices were used, and the scanning time was approximately 3–5 minutes for four sections: three sections for visualization of the right coronary artery, left main trunk, left anterior descending branch and left circumflex branch and one section for visualization of the root of the left main trunk, left anterior descending branch, and left circumflex branch simultaneously. Thus, the overall scanning time was approximately 15–30 minutes. For whole-heart imaging, 130–150 axial slices covered the entire heart. Because this technique covers the entire heart at once, one section is imaged in approximately 20–30 minutes.

With reference to the coronal image of the survey scan, the axial plane for cine MRI was set to the center of the heart. After the heart phase of the patient was defined, the scan was started. Because the patient was asleep, the scan was obtained under normal respiration. The short-axis image of the right coronary artery was obtained, and by evaluation of the diastolic rest period of phase 80, the trigger-delay program was set to acquire the data for three-point-plan scanning or whole-heart imaging.

Results

The imaging examination was successful for 34 of the 35 patients, a success rate of 97%. The 35th patient was wearing an undershirt with a metallic zipper that had not been noticed. Among 525 segments, 313 (60%) were evaluated. The visualization rate of the coronary arteries was 97% for segment 1, 97% for segment 2, 89% for segment 3, and 57% for segment 4 in the right coronary artery; 97% for segment 5 in the left main trunk; 97% for segment 6, 86% for segment 7, 43% for segment 8, 8.6% for segment 9, and 5.7% for segment 10 in the left anterior descending branch; and 91% for segment 11, 5.7% for segment 12, 54% for segment 13, 34% for segment 14, and 31% for segment 15 in the left circumflex branch (Fig. 1). Comparison of the visualization rate of the peripheral coronary arteries (segments 4, 7, 8, and 12–15) with three-point-plan scanning and whole-heart imaging indi-

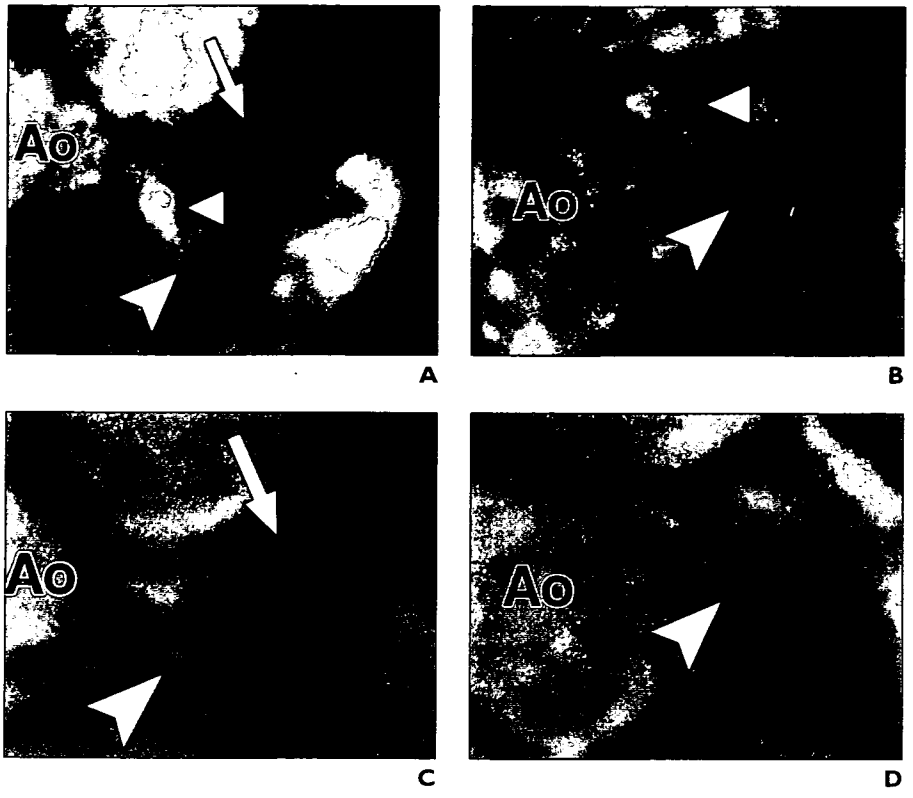

Fig. 2—1-year-5-month-old boy with Kawasaki disease. Ao = aorta.
A and **B**, MR coronary angiograms obtained with cardiac coil made for adults while disease is in acute stage shows left anterior descending branch (*arrow*, **A**), left circumflex branch (*arrowhead*), and aneurysm at bifurcation of left coronary artery (*triangle*). Although aneurysm is evident, image is not clear.
C and **D**, MR coronary angiograms obtained with Flex-M coil (Philips Medical Systems) while disease is in convalescent stage shows left anterior descending branch (*arrow*, **C**), and left circumflex branch (*arrowhead*). Regression of aneurysm was verified. Image is clear and shrinkage of aneurysm is evident.

cated that the rate of visualization with whole-heart imaging (54.4%) was greater than that with three-point-plan scanning (35.8%) ($p < 0.01$). The rate of visualization of the dilated coronary arterial lesions of 18 segments in 12 coronary arterial lesions had a sensitivity of 94.7%, specificity of 98.8%, positive predictive value of 94.7%, negative predictive value of 98.8%, and accuracy of 98.1%.

Patient 1 was a boy 1 year 5 months old who weighed 8.8 kg and had a heart rate of 105 BPM. MR CAG with a synergy cardiac coil performed on the 21st day of illness (Figs. 2A and 2B) depicted an aneurysm at the root of the left circumflex branch of the left coronary artery. The peripheral coronary arteries of the left anterior descending branch and the left circumflex branch also were identified. However, the spatial resolution of the image was low, so the image was not clear. To verify regression of the aneurysm after an interval of 3 months, MR CAG was repeated with a Flex-M coil (Philips Medical Systems), and regression was clearly visualized (Figs. 2C and 2D). Moreover, image quality improved because of a high signal-to-noise ratio, and the left circumflex branch was clearly visualized.

Patient 2 was a boy 3 years 11 months old who weighed 15.3 kg and had a heart rate of 113 BPM. CAG was performed because of giant coronary aneurysms on the left coronary artery (segments 5–7), right coronary artery (segments 1–4), and left circumflex branch (segment 11) (Figs. 3A and 3B). MR CAG was performed 3 days later, on the 90th day of illness (Figs. 3C–3H). The giant coronary aneurysms were clearly visualized with MR CAG, the findings of which showed excellent agreement with the CAG findings.

Patient 3 was a boy 5 years 7 months old who weighed 16.6 kg and had a heart rate of 70 BPM. MR CAG was performed 47 months after the onset of KD. A dilated lesion on the left coronary artery (segment 6) was visualized clearly with all methods of MRI (Fig. 4).

Discussion

KD has an unknown origin, and it usually occurs in infants and children younger than 4 years [11]. In Japanese patients, coronary aneurysms develop in the acute phase in 16% of patients and remain in 5% as a sequela after the convalescent phase. These aneurysms decrease in size soon after the acute stage and often regress completely within 2 years, but some develop to occlusion or localized stenosis of the artery even 10 or 20 years after the onset of the disease [1]. To predict the progress of the disease and determine appropriate treatment and follow-up protocols, it is essential to understand the size and shape of the aneurysms in the early phase. Therefore, invasive CAG should be performed as soon as possible after the acute stage [2]. However, CAG poses high risk to young children with KD. Furthermore, patients need follow-up with frequent CAG throughout their lives. A noninvasive method of visualizing aneurysms immediately after the acute phase, and thrombus and the coronary arteries during follow-up, has long been needed.

We have been performing noninvasive coronary artery imaging with MRI since 2000 and have conducted follow-up of the coronary arteries of patients with KD [9, 16]. At first we used 3D fast low-angle shot [17] and 3D magnetization-prepared rapid acquisition gradient-echo imaging [18–20] with contrast agents and with breath-hold (30 seconds) to image the coronary artery. Later we were able to image the coronary arteries without contrast agents by using the true fast imaging with SSFP sequence [21]. This examination, however, is not suitable for infants and young children, who cannot hold their breath for imaging. However, with the invention of the navigator echo technique, coronary artery imaging can be performed during free breathing [6, 9].

Although there are many reports of MR CAG of adults [4–7, 22], to our knowledge there have been no reports, except for those by our group [7, 8, 15, 16], of MR CAG of infants. We have performed MR CAG on more than 200 patients with coronary artery lesions due to KD. It is very difficult, however, to visualize the coronary arteries of young children compared with those of adults. We have optimized the receiver coils and the exact data acquisition technique to improve the visualization rate of MR CAG of infants and children.

Children younger than 6 years have small bodies and narrow coronary arteries. It became clear that the cardiac coil we were using was not suitable for these children. Image tur-

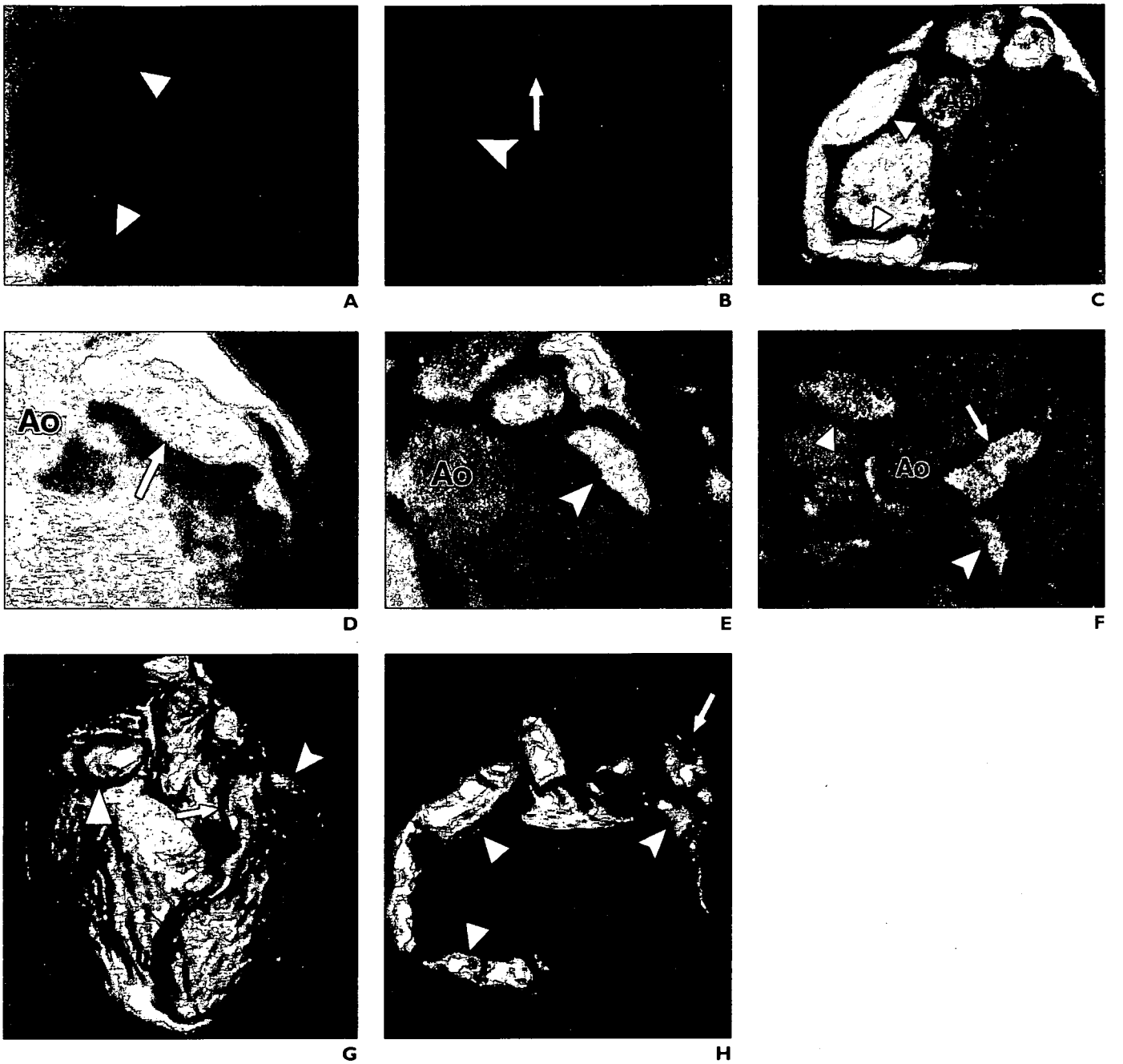

Fig. 3—3-year-11-month-old boy with Kawasaki disease and giant coronary aneurysms of segments 1–7 and 11.
A, Coronary angiogram of right coronary artery shows aneurysm (*triangles*).
B, Coronary angiogram of left coronary artery shows aneurysms of left anterior descending branch (*arrow*) and left circumflex branch (*arrowhead*).
C, Maximum-intensity-projection whole-heart coronary angiogram obtained 3 days after **A** and **B** shows aneurysm (*triangles*) on right coronary artery. Ao = aorta.
D, Maximum-intensity-projection whole-heart coronary angiogram obtained in same examination as **C** shows left anterior descending branch (*arrow*). Ao = aorta.
E, Maximum-intensity-projection whole-heart coronary angiogram obtained in same examination as **C** and **D** shows left circumflex branch (*arrowhead*). Ao = aorta.
F, Soap-bubble maximum-intensity-projection image shows all three branches in one plane. Triangle indicates right coronary artery; arrow, left anterior descending branch; arrowhead, left circumflex branch. Ao = aorta.
G and **H**, Reconstructed volume-rendered images (**G**, whole heart; **H**, heart removed and remaining coronary arteries) show aneurysms at segment 1 in right coronary artery (*triangles*), left anterior descending artery (*arrow*), and left circumflex artery (*arrowhead*).

bulence occurred because the coil did not maintain high spatial resolution. In contrast, the Flex-M coil is suitable for small children and improved visualization of the coronary artery with high spatial resolution and a high signal-to-noise ratio. Head coils or knee coils previously were used to image the thorax and abdomen of young children. Because these are single coils, we could not perform parallel

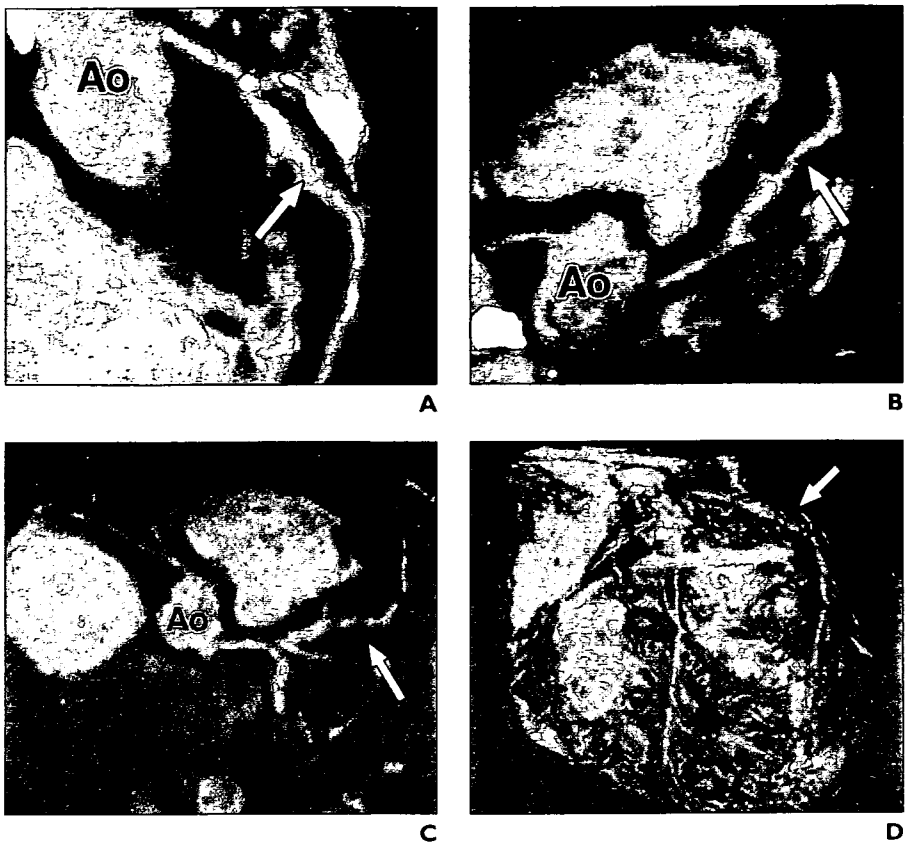

Fig. 4—5-year-7-month-old boy with Kawasaki disease. Dilated lesion (*arrow*) was visualized on left anterior descending branch (segment 6) on all reconstructed images.
A and **B**, Coronal oblique (**A**) and axial oblique (**B**) maximum-intensity-projection images. Ao = aorta.
C, Soap-bubble maximum-intensity-projection image. Ao = aorta.
D, Volume-rendered image.

imaging. It is well known that parallel imaging can be effective in many ways, such as coil sensitivity correction, reduction of scanning time, and high-resolution imaging [17]. We therefore used the Flex-M coil for parallel imaging to maintain spatial and time resolution and succeeded in improving visualization of the coronary arteries in children.

In infants, the heart and coronary arteries are small, the heart rate is high, and the heart is moving at all times. To image the coronary arteries accurately under these conditions, it is important to set the vectorcardiographic gating parameters exactly so that blurring induced by heartbeats is minimized and excellent images are obtained. To identify motion of the heart, we performed retrospective cine MRI (50–80 phases). We then tried to acquire data during the diastolic rest period with cine MRI. We were able to obtain coronary artery images as high-resolution 3D data by collecting the data only at the expiration position without breath-hold. The navigator echo technique conventionally allows extension of scanning time, which is why breath-hold scans are widely used. However, with the invention of parallel imaging, it has become possible to reduce scanning time, and the navigator echo technique has become the more widely used coronary artery imaging technique. Because breath-hold is not necessary with this technique, it was possible to perform MR CAG on the children in our study. Moreover, with correct setting of the parameters, the coronary arteries were visualized in children with heart rates greater than 100 BPM. The examination success rate was 97%.

Because 3D volume data on the entire heart are obtained as CT images in whole-heart imaging, the data from any section or direction can be reconstructed and visualized. Moreover, the rate of visualization of the peripheral coronary arteries in children is better with whole-heart imaging than with three-point-plan scanning.

If several techniques are used, it is possible to obtain high-resolution coronary artery images as 3D whole-heart images with SSFP. The techniques can be performed noninvasively without contrast enhancement and without a breath-hold. The images obtained can be reconstructed and every section of the coronary arteries visualized, which is impossible with CAG. MR CAG is a useful method of evaluating coronary arterial lesions in children with KD, even those younger than 6 years.

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原　著

MCP-1, *CCR2*遺伝子多型が川崎病の各病態に及ぼす影響

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Key words :
Kawasaki disease, gene polymorphism, MCP-1, CCR2

How *MCP-1* A-2518G and *CCR2* G190A Polymorphism Interfere with Kawasaki Disease

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Background: We have already demonstrated the high expression of monocyte chemoattractant protein-1 (*MCP-1*) in the acute phase of Kawasaki disease (KD). We examined how *MCP-1* and its receptor, *C-C chemokine receptor 2* (*CCR2*), gene polymorphism affect the clinical course of KD.
Methods: KD patients (n = 184, 2.8 ± 0.2 years old) were enrolled in this study. The gene polymorphism of *MCP-1* A-2518G and *CCR2* G190A were determined, and we compared the febrile period, effectiveness of immunoglobulin (IVIG) therapy, maximum peripheral blood white blood cell count, maximum C-reactive protein level, and the occurrence of coronary artery disturbances among KD patients.
Results: The G/G allele in *MCP-1* A-2518G polymorphism has a longer febrile period (7.9 ± 3.4 vs. 9.5 ± 5.6 days, p = 0.033) and tends to be resistant to IVIG therapy (p = 0.086). We did not find any significant differences in *CCR2* G190A polymorphism.
Conclusion: *MCP-1* polymorphism is closely related to the febrile period of acute KD.

要　旨

目的：*Monocyte chemoattractant protein-1* (*MCP-1*)，およびその受容体*C-C chemokine receptor 2* (*CCR2*)遺伝子多型が，川崎病臨床経過をいかに修飾しているのかを検討した．
方法：川崎病既往児184例における*MCP-1* A -2518G，*CCR2* G190A遺伝子多型を解析した．川崎病急性期における発熱期間，免疫グロブリン療法(IVIG)解熱効果，最大白血球数，最大CRP値，冠動脈障害の有無を比較検討した．
結果：*MCP-1* A-2518G遺伝子多型では，G/G症例の発熱期間が有意に延長し(7.9 ± 3.3 vs. 9.5 ± 5.6日，p = 0.033)，IVIGの解熱効果も認めにくい傾向があった(p = 0.086)．*CCR2* G190A遺伝子多型では有意な差異は認められなかった．
結語：*MCP-1* A-2518G遺伝子多型は川崎病急性期の発熱期間に関連している．

緒　言

ゲノムプロジェクトが進行し，2002年にヒトの全ゲノムが明らかにされて以来，遺伝子の研究はその機能の解明へと推移している．ヒトとチンパンジーの遺伝子塩基配列の差はわずか1.2%程度に過ぎず，ましてヒトとヒトの間でのゲノムの差となると極めてわずかなものとなる．同種間の遺伝子塩基配列の差異を遺伝子多型(polymorphism)と呼び，あらゆる疾患において遺伝子多型が，かかりやすさ，重症度，薬剤への反応性など，これまで個々人の「体質」と考えられてきた事柄のバックグラウンドとなっている可能性がある．遺伝子

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Table 1 Polymerase chain reaction (PCR)

Polymorphism (Gene Bank Code)	Primers	PCR product length	Restriction enzyme
MCP-1 A-2518G	Forward: 5'GCC GAG ATG TTC CCA GCA CAG3'	932 bp	*Pvu*II
(AF519531)	Backward: 5'CCC TGC TTT GCT TGT GCC TCT T3'		
CCR2 G190A	Forward: 5'TTG TGG GCA ACA TGA TGG3'	196 bp	*Bsa*BI
(U95626)	Backward: 5'ATG TGA TAC AGC CCT GTG AAT AA3'		

多型と疾患との関係が解明されれば，個々人に応じた疾患の予防，治療のための適切な薬剤の選択や薬剤量の調節など，臨床と直結した重要な情報を提供できる可能性がある．日本でも遺伝子多型の研究推進のため，文部科学省リーディングプロジェクトとして「オーダーメイド実現化プロジェクト」と名付けられた大規模な研究が進行中で，47疾患を対象に30万人規模のゲノムDNA解析を目標として，全国の12医療施設が患者から血液検体を収集しているところである（http://www.biobankjp.org/）．

川崎病に関する遺伝子多型の報告も認められるようになってきている[1-3]．われわれの施設でも川崎病における遺伝子多型を解析しており，これまでにも*angiotensine*変換酵素deletion/ insertion多型のD alleleを有する症例や*angiotensin II receptor 1*（*AT1R*）A1166C多型のC alleleを有する症例では，川崎病冠動脈障害のなかでも狭窄性病変を来すリスクが高くなることを報告してきた[4]．一方，われわれは川崎病急性期血清では白血球走化因子であるmonocyte chemoattractant protein-1（MCP-1）濃度が上昇し，末梢血単核球細胞では*MCP-1*のmRNAが著しく亢進していることを見いだしている[5]．MCP-1には*MCP-1* A-2518Gの遺伝子多型が報告され，G/G alleleでは血中MCP-1濃度が上昇しており[3]，成人においてはG/G alleleと冠動脈疾患との関連が指摘されている[6]．さらにMCP-1の受容体であるC-C chemokine receptor 2（CCR2）にも*CCR2* G190Aというアミノ酸変異を伴う遺伝子多型が認められ，変異部ではバリンがイソロイシンに変異している（*CCR2* V64I）．*CCR2* G190A遺伝子多型と循環器疾患との関係についてはA alleleが心筋梗塞のリスクアレルであるとする報告[7]やG alleleがA alleleに比べ冠動脈石灰化が大きいとする報告[8]，関係ないとする報告[9]などがあり，いまだ議論の多いところである．MCP-1のシグナル伝達の中心である受容体であるため，今後とも研究が積み重ねられていくことと思われる．

このように*MCP-1*やMCP-1と関係する遺伝子は，冠動脈疾患や川崎病急性期における病態形成に密接な関係があることが示唆される．われわれは川崎病における*MCP-1* A-2518G遺伝子多型およびその受容体である*CCR2* G190A遺伝子多型を解析し，発熱期間，免疫グロブリン療法への反応，冠動脈病変の有無などの川崎病の病態と比較検討した．

対象・方法

保護者より書面による了解の得られた川崎病既往症例184例（2.8 ± 0.2歳）を対象とした．本研究は日本医科大学倫理委員会，および各共同研究施設の倫理委員会の了承を得た研究である．末梢血白血球よりDNA Blood Mini Kit（QIAGEN，CA，USA）を用いてDNAを抽出し，polymerase chain reaction（PCR）法により遺伝子多型部位を増幅，増幅されたDNAを制限酵素に反応させ遺伝子多型の有無を鑑別した．各遺伝子多型に対するプライマー，PCRにて増幅されるDNA塩基の長さ，制限酵素をTable 1に示す．Applied Biosystems（Foster City，CA，USA）9700 PCR systemを用いて，10ng DNA，5pMの各プライマー，0.25mM dNTP，1.5mM MgCl2，および1.5U Taq polymerase（Takara Bio Inc.，Ohtsu，Japan）にてPCRを行った．PCRの反応は，*MCP-1* A-2518Gの遺伝子多型では，94°C30秒，72°C60秒のPCRサイクルを5回，94°C30秒，70°C60秒のPCRサイクルを5回，94°C30秒，68°C60秒のPCRサイクル25回行った．また，*CCR2* G190A遺伝子多型では94°C30秒，52°C30秒，72°C 1分のPCRサイクルを35回行った．得られたそれぞれのプライマーによるPCR産物は，制限酵素*Pvu*II，*Bsa*BI（New England Biolabs，MA，USA）を用いてそれぞれ37°C，60°Cにて2時間反応させた．この結果，*MCP-1* A-2518G多型では得られたPCR産物（932bp）がG alleleを有する場合に709bpと223bpに分解され，*CCR2* G190A遺伝子多型では得られたPCR産物（196bp）がA allele（変異の結果，バリンがイソロイシンとアミノ酸が変異する）を有する場合に178bpと18bpに分解され，それぞれ1.5%および4%のアガロースゲルにて電気泳動することで遺伝子多型の同定を行った（Fig. 1）

それぞれの遺伝子多型において，発熱期間，免疫グロブリン療法（IVIG）の解熱効果（IVIG終了後2日以内の

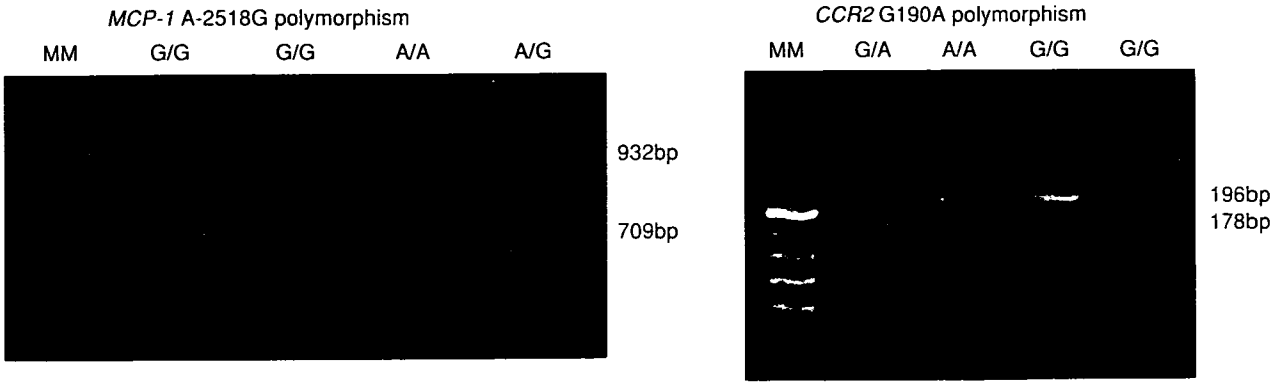


Fig. 1 *MCP-1* A-2518G and *CCR2* G190A polymorphism detection.
PCR product lengths of *MCP-1* A-2518G and *CCR2* G190A polymorphism were 932 bp and 196 bp, respectively. When the sequence of *MCP-1* has the G allele, the PCR product is digested by restriction enzyme *Pvu*II into 709 bp and 223 bp. When there is an A allele in *CCR2*, restriction enzyme *Bsa*BI digests the PCR product into 178 bp and 18 bp.
MM: molecular marker, G: guanine, A: adenine

解熱を「解熱効果あり」とした)，川崎病経過中の最大白血球数，最大CRP値，一過性拡張を含めた冠動脈障害の有無を比較検討した．

1．統計

それぞれの遺伝子多型のIVIG効果および冠動脈障害の有無の判定では有意差はχ^2 testを用いて確認し，有意と判定された場合はオッズ比，95%信頼区間を算出した．また，症例数が10以下の場合はFisher's exact testを用いた．$p<0.05$をもって有意と考えた．有熱期間，最大白血球数，最大CRP値においては，One way ANOVAを用い，有意差を認めた場合にはpost hoc testにて確認した．数値は平均±SEをもって表現した．統計の算出には，統計ソフトStatView 5.0(SAS Institute Inc., NC, USA)を用いた．

結　果

今回の方法により遺伝子多型を同定できたのは，*MCP-1* A-2518G多型では184例中166例，*CCR2* G190A多型では184例中178例であった．分類された各遺伝子型は以下のとおりである．

MCP-1 A-2518G多型：A/A 16.3%(27例)，A/G 54.8%(91例)，G/G 28.9%(48例)

CCR2 G190A多型：A/A 5.1%(9例)，A/G 38.2%(68例)，G/G 56.7%(101例)

各遺伝子多型の間に，男女比，年齢の有意差はなかった．

1．最大白血球数(Fig. 2A1, 2)

MCP-1 A-2518G多型(Fig. 2A1)：A/A(n=27)14,800±842，A/G(n=91)15,400±530，G/G(n=48)16,700±1,047，*CCR2* G190A多型(Fig. 2A2)：A/A(n=9)14,200±1,007，A/G(n=68)15,400±647，G/G(n=101)16,100±593であり，各遺伝子多型との間において最大白血球数の有意差は認めなかった．

2．最高CRP値(Fig. 2B1, 2)

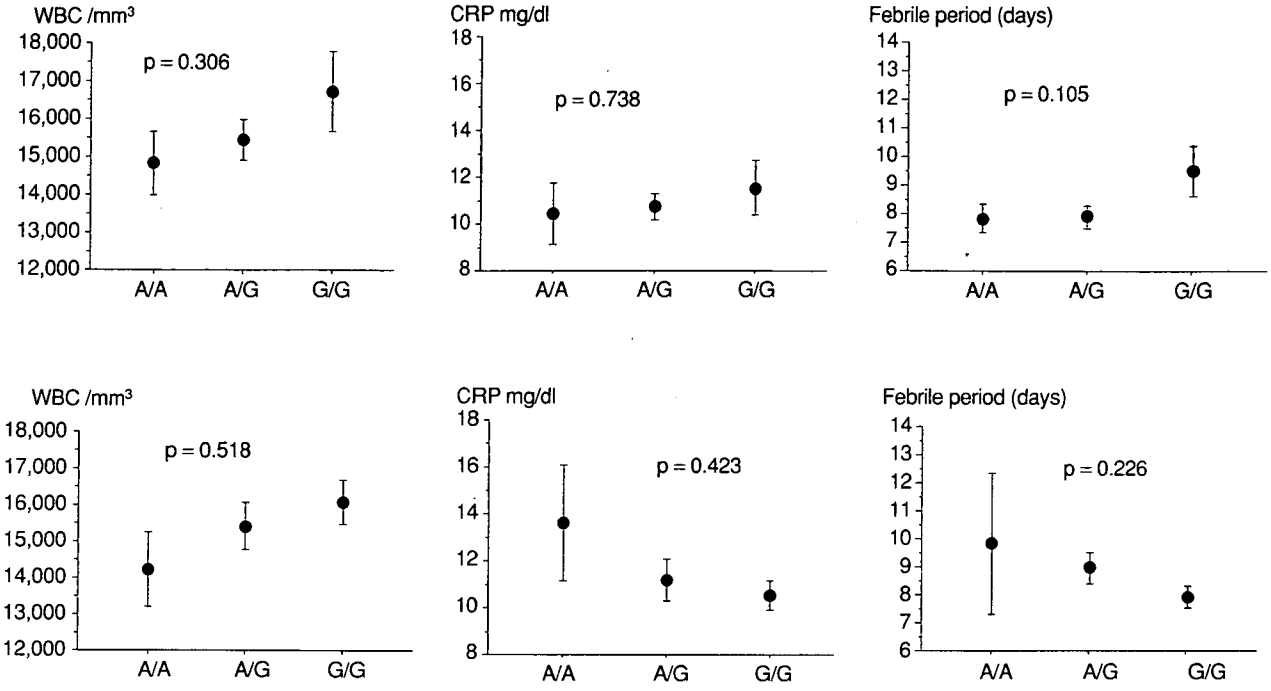
MCP-1 A-2518G多型(Fig. 2B1)：A/A(n=27)10.5±1.3 mg/dl，A/G(n=89)10.6±0.6 mg/dl，G/G(n=47)11.3±1.2 mg/dl，*CCR2* G190A多型(Fig. 2B2)：A/A(n=8)13.6±2.4 mg/dl，A/G(n=67)11.2±0.9 mg/dl，G/G(n=100)10.5±0.6 mg/dlであり，各遺伝子多型との間において最大CRP値の有意差は認められなかった．

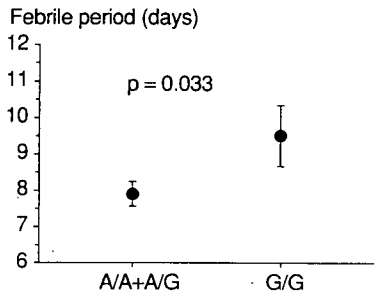
3．発熱期間(Fig. 2C1, 2, 2D)

MCP-1 A-2518G多型(Fig. 2C1)：A/A(n=25)7.9±0.5日，A/G(n=81)7.9±0.4日，G/G(n=44)9.5±0.8日，*CCR2* G190A多型(Fig. 2C2)：A/A(n=7)9.9±2.5日，A/G(n=64)9.0±0.6日，G/G(n=91)7.9±0.4日であった．*MCP-1* A-2518G多型，*CCR2* G190A多型ともに有意差は認められなかったが(Fig. 2C1, 2)，*MCP-1* A-2518G多型をさらにA/AまたはA/G alleleとG/G alleleとに分けて解析してみるとG/G alleleの発熱期間が有意に延長していた(7.9±0.3日 vs. 9.5±0.8日，$p=0.033$)(Fig. 2D)．

4．IVIGの解熱効果(Table 2)

MCP-1 A-2518G多型：「解熱効果あり」がA/A(n=22)91.7%，A/G(n=69)94.5%，G/G(n=30)83.3%であり，「解熱効果なし」がA/A(n=2)8.3%，A/G(n=4)5.5%，





A1	B1	C1
A2	B2	C2
D		

Fig. 2 White blood cell count, CRP level, and febrile period on *MCP-1* A-2518G and *CCR2* G190A polymorphism.
Details of the white blood cell count of *MCP-1* A-2518G polymorphism were as follows: A1: A/A (n = 27) 14800 ± 842, A/G (n = 91) 15400 ± 530 and G/G (n = 48) 16700 ± 1047. Those of *CCR2* G190A polymorphism were as follows: A2: A/A (n = 9) 14200 ± 1007, A/G (n = 68) 15400 ± 647 and G/G (n = 101) 16100 ± 593. There were no significant differences (p = 0.306 and p = 0.518, respectively).
The CRP levels of *MCP-1* A-2518G polymorphism were as follows: B1: A/A (n = 27) 10.5 ± 1.3 mg/dl, A/G (n = 89) 10.6 ± 0.6 mg/dl, and G/G (n = 47) 11.3 ± 1.2 mg/dl. Those of *CCR2* G190A polymorphism were as follows: B2: A/A (n = 8) 13.6 ± 2.4 mg/dl, A/G (n = 67) 11.2 ± 0.9 mg/dl, and G/G (n = 100) 10.5 ± 0.6 mg/dl. No significant differences were detected (p = 0.738 and p = 0.423, respectively).
The febrile period also showed no significant differences among *MCP-1* A-2518G and *CCR2* G190A polymorphism (p = 0.105 and p = 0.226, respectively). The details of each polymorphism were as follows: *MCP-1* A-2518G polymorphism (C1): A/A (n = 25) 7.9 ± 0.5 days, A/G (n = 81) 7.9 ± 0.4 days, and G/G (n = 44) 9.5 ± 0.8 days, and *CCR2* G190A polymorphism (C2): A/A (n = 7) 9.9 ± 2.5 days, A/G (n = 64) 9.0 ± 0.6 days and G/G (n = 91) 7.9 ± 0.4 days.
When the A/A allele, together with the A/G allele, were compared to the G/G allele in *MCP-1* A-2518G polymorphism, the febrile period was significantly longer in the G/G allele (7.9 ± 0.3 vs. 9.5 ± 0.8 days, p = 0.033) (D).

G/G (n = 6) 16.7%であった．有意差は認めなかったが (p = 0.158)，G/G alleleに「解熱効果なし」がやや高い印象があるため，G/G alleleとその他のalleleに分割して比較してみたところ，A/A + A/G allele症例でIVIGの「解熱効果ありが」93.8% (n = 91)，「解熱効果なし」が6.2% (n = 6) であったのに対して，G/G allele症例では「解熱効果あり」83.3% (n = 30)，「解熱効果なし」16.7% (n = 6) と，G/G alleleを有する症例で解熱効果を認めない傾向がより高くなった (p = 0.086，Fisher's exact test)．

CCR2 G190A多型ではA/A allele症例でのIVIG「解熱効果なし」の症例がなかったため，A/A allele症例とA/G allele症例を合わせてG/G allele症例と比較した．A/AまたはA/G allele症例ではIVIG「解熱効果あり」が91.9% (n = 57)，「解熱効果なし」が8.1% (n = 5) であったのに対して，G/G allele症例では「解熱効果あり」が91.4% (n = 74)，「解熱効果なし」が8.6% (n = 7) と有意差は認められなかった (p > 0.99，Fisher's exact test)．

5. 冠動脈障害の有無

MCP-1 A-2518G多型では冠動脈障害を認めた症例はA/A 22.2%(n=6)，A/G 19.8%(n=18)，G/G 22.9%(n=11)で，冠動脈障害がなかった症例はA/A 77.8%(n=21)，A/G 80.2%(n=73)，G/G 77.1%(n=37)であった．また*CCR2* G190A多型では，冠動脈障害を認めた症例はA/A 22.2%(n=2)，A/G 25.0%(n=17)，G/G 19.8%(n=20)であり，冠動脈障害を認めなかった症例はA/A 77.8%(n=7)，A/G 75.0%(n=51)，G/G 80.2%(n=81)であった．どちらの遺伝子多型とも冠動脈障害との有意な相関は認められなかった．

Table 2 Effectiveness of immunoglobulin therapy

MCP-1 A-2518G

	A/A and A/G	G/G
Effective	93.8% (91)	83.3% (30)
Not effective	6.2% (6)	16.7% (6)*

*p = 0.086

CCR2 G190A

	A/A and A/G	G/G
Effective	91.9% (57)	91.4% (74)
Not effective	8.1% (5)	8.6% (7)

p > 0.99

考　案

MCP-1 A-2518G遺伝子多型でのG alleleは，MCP-1のより高い血中濃度と相関することが報告されている[10]．さらに，3,236例を対象としたFramingham Heart StudyにおいてもG alleleのより高いMCP-1血中濃度，および心筋梗塞の発症との相関が報告されたばかりである[6]．Jibikiら[3]の報告によれば，日本人の血中単核球細胞におけるInterleukin-1β刺激に対するMCP-1産生反応が，G allele保有者のほうがより高いとされ，川崎病患児の急性期でもG allele保有者がより高いMCP-1血中濃度を呈する傾向があるようである．また，川崎病急性期の単核球細胞でのMCP-1 mRNA濃度とMCP-1血中濃度は上昇しており，大量IVIGにより抑制されることも認められている[5]．したがって，*MCP-1* A-2518G遺伝子多型と川崎病との何らかの関係が示唆されることから，今回われわれはこのような研究を行うに至った．今回の研究では，G/G alleleを有する症例の発熱期間が有意に延長し(p=0.033)，IVIGの解熱効果も乏しい傾向があった(p=0.086)．IVIGにより急激に川崎病急性期患児の血中MCP-1濃度が低下する[5, 11]ことから，基礎的MCP-1濃度が高いG/G症例[3, 6]では，川崎病の発熱期間やIVIG解熱効果に影響することは推測される．MCP-1は炎症性ケモカインであり，炎症と密接に関係する以上，「解熱しない」ということは炎症の強さとの非特異的な関係の結果である可能性も否定できない．しかしながら，今回の研究では同時に最大白血球数やCRP値に有意な差は認めていないことから，非特異的な炎症の強さだけではなく，川崎病の経過において*MCP-1*の遺伝子そのものが「解熱しない」ことに寄与する可能性が考えられる．このように本研究により初めて*MCP-1* A-2518G遺伝子多型でのG/G alleleが川崎病発熱期間，IVIGによる解熱効果といった病態にかかわることが示唆された．

一方，MCP-1の受容体であるCCR2の遺伝子多型である*CCR2* G190A遺伝子多型解析では，本研究において川崎病の各病態の指標において各allele間で有意差は認められなかった．Bjarnadottirら[9]の成人1,842例の検討では心筋梗塞とA/A alleleとの間に有意な関係は認めていない．心筋梗塞とA/A alleleとの有意な関係を認めたOrtleppら[7]のより若い65歳以下の1,454例の検討でもOR1.47，95%CI 1.16～1.87とodds比はそれほど高くなく，大規模な症例集積で初めて検証が可能であった．Marenbergら[12]によれば若年であるほど疾患・病態の遺伝子的関与が強くなるともされている．今回症例は少ないが，年齢別に分けると*CCR2* A alleleを有する例が若年例で有熱期間が長くなる傾向もあり，今後われわれの研究でも症例数を重ねていけば*CCR2* G/A遺伝子多型との有意な関係が立証されるかもしれない．

また，今回冠動脈病変に関しては遺伝子多型との相関は認められなかったが，*MCP-1*遺伝子多型G alleleが川崎病の重症度判定の一つである「解熱しない」ことに関与している以上，冠動脈病変形成に何らかの影響を及ぼしていることが推察されるので，今後とも本研究を継続していきたい．

今回の研究で初めて川崎病の病態に*MCP-1*遺伝子多型という遺伝子的バックグランドが関与していることを証明した．今後川崎病症例の遺伝子多型の研究が進んでいけば，遺伝子的に川崎病の重症度や薬物効果をあらかじめ予測できる可能性がある．どの遺伝子がどのような影響を川崎病に与える可能性があるのか，「オーダーメイド実現化プロジェクト」に川崎病も対象とするなど，全国的に症例を集積した大規模な研究を遂行するシステムを早急に確立することが求められる．そして，遺伝子的なバックグランドから当初のIVIGが無効

な場合，やみくもに免疫グロブリン追加投与を行うよりはステロイド療法や血漿交換，抗tumor necrosis factor-α療法といった治療法を優先させたほうが治療効果の面からも，また医療経済的側面からも良いという結論がだされるのかもしれない．今後の遺伝子研究の発展が期待されるところである．

なお，本論文の要旨は第41回日本小児循環器学会学術総会で発表し，座長からの推薦を受けて投稿したものである．

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