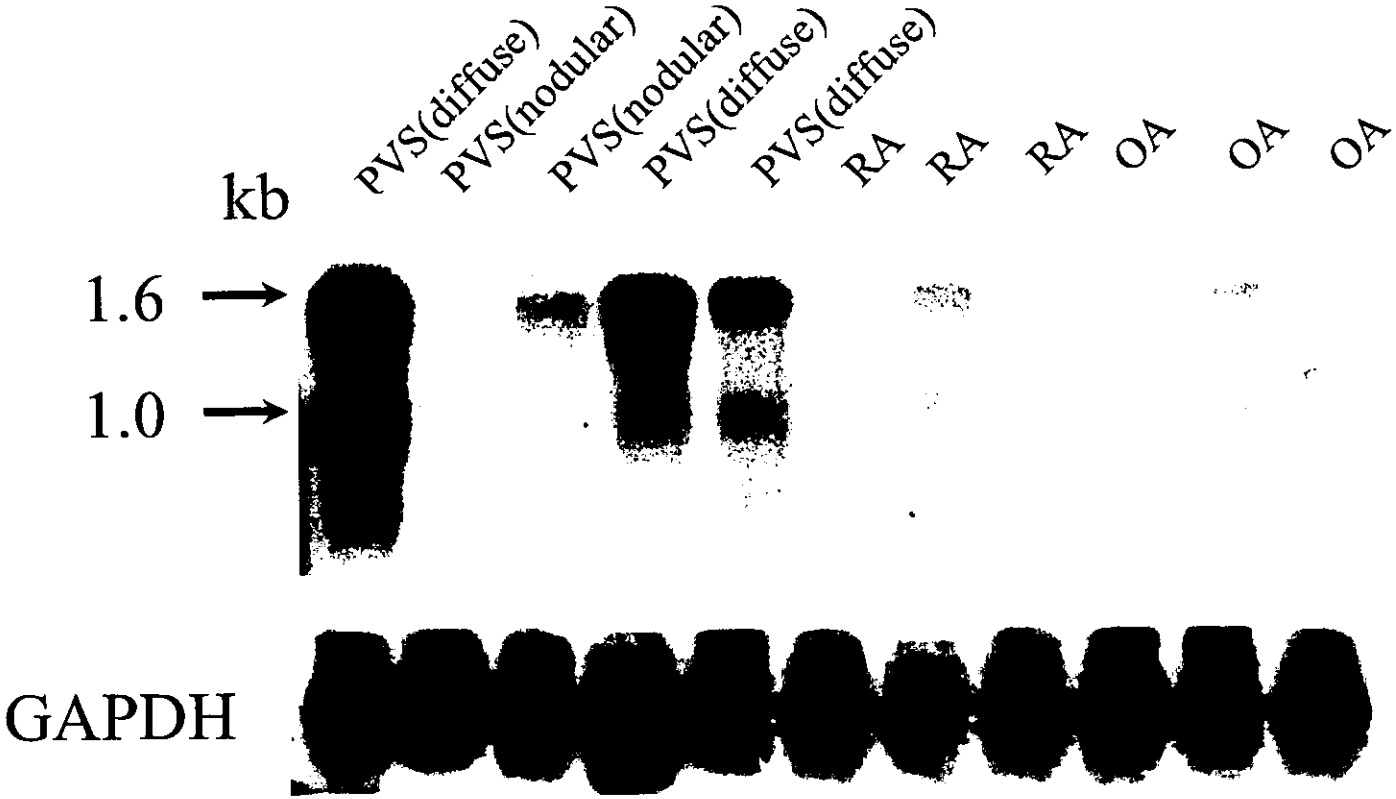
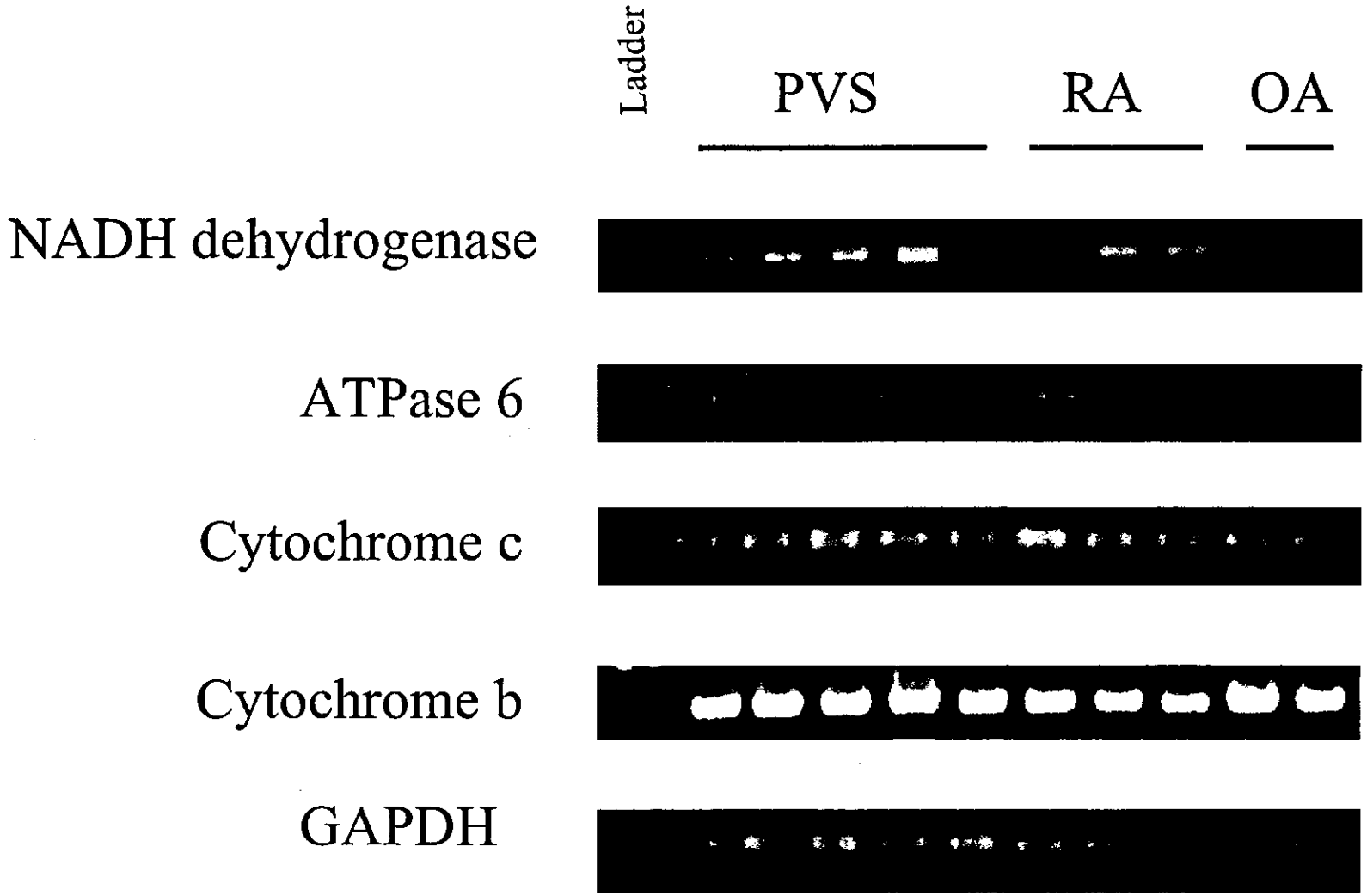


Figure 2. Kosei Ijiri



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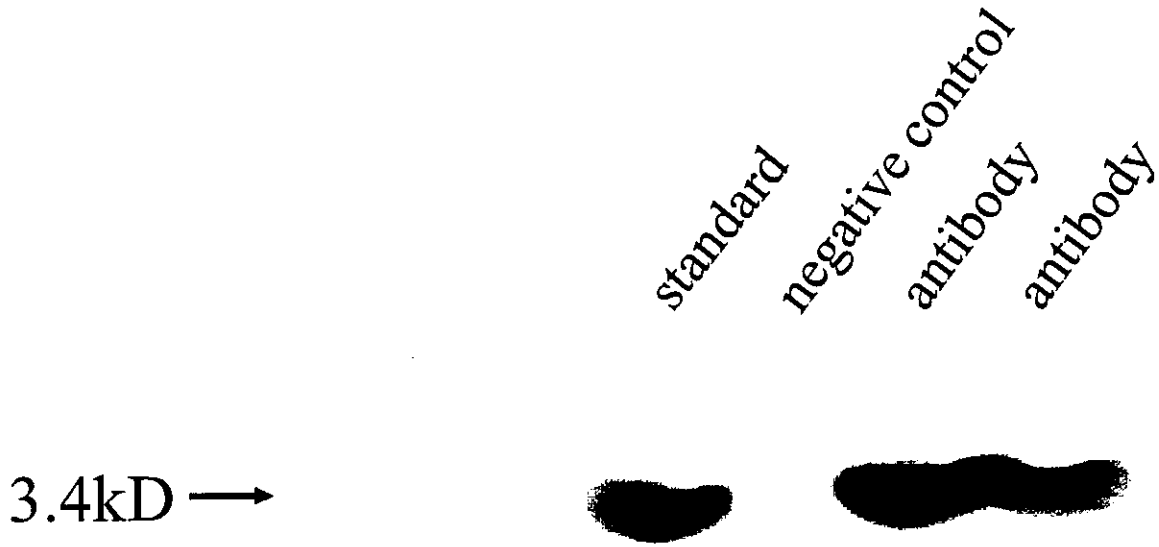

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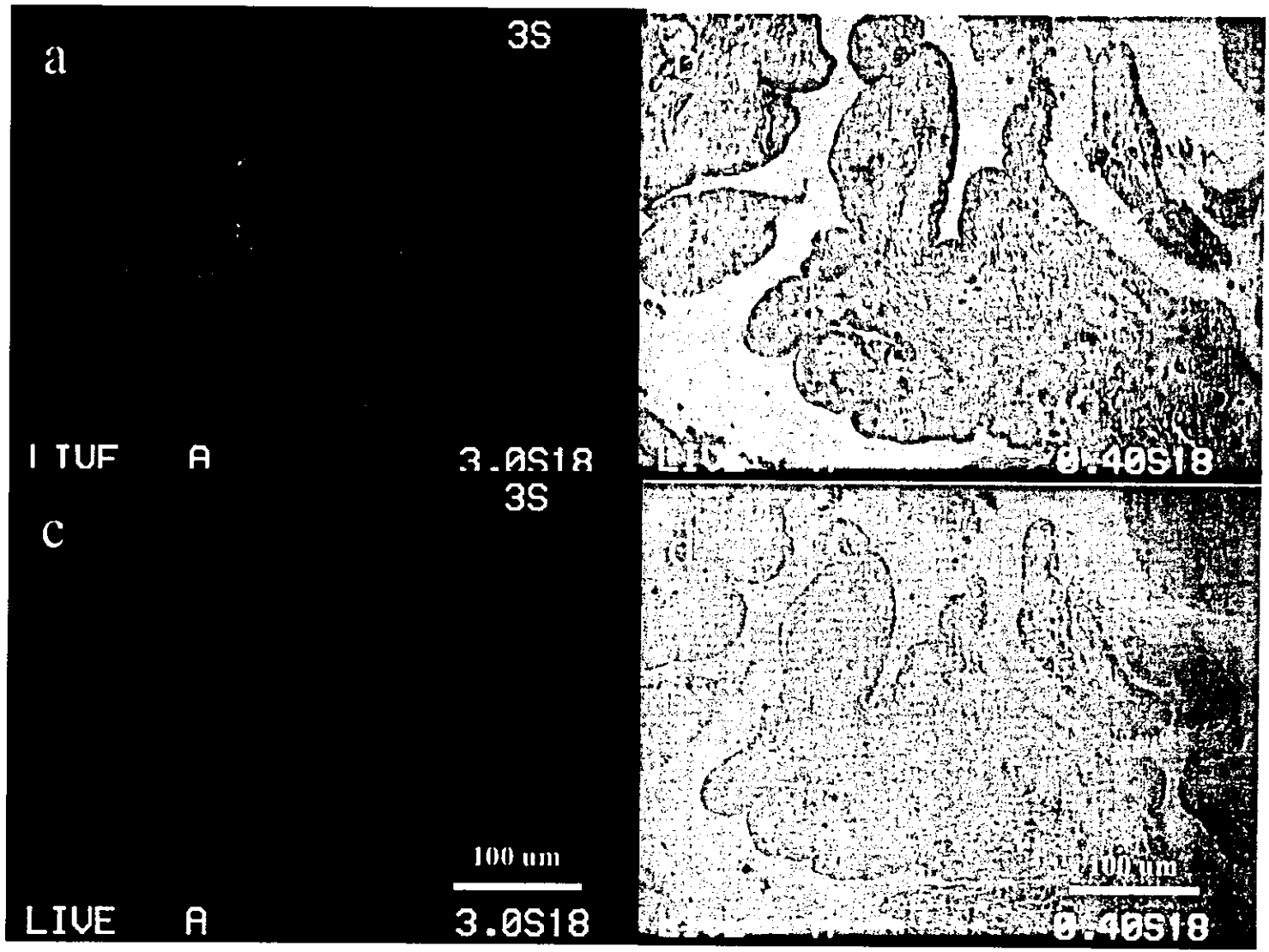

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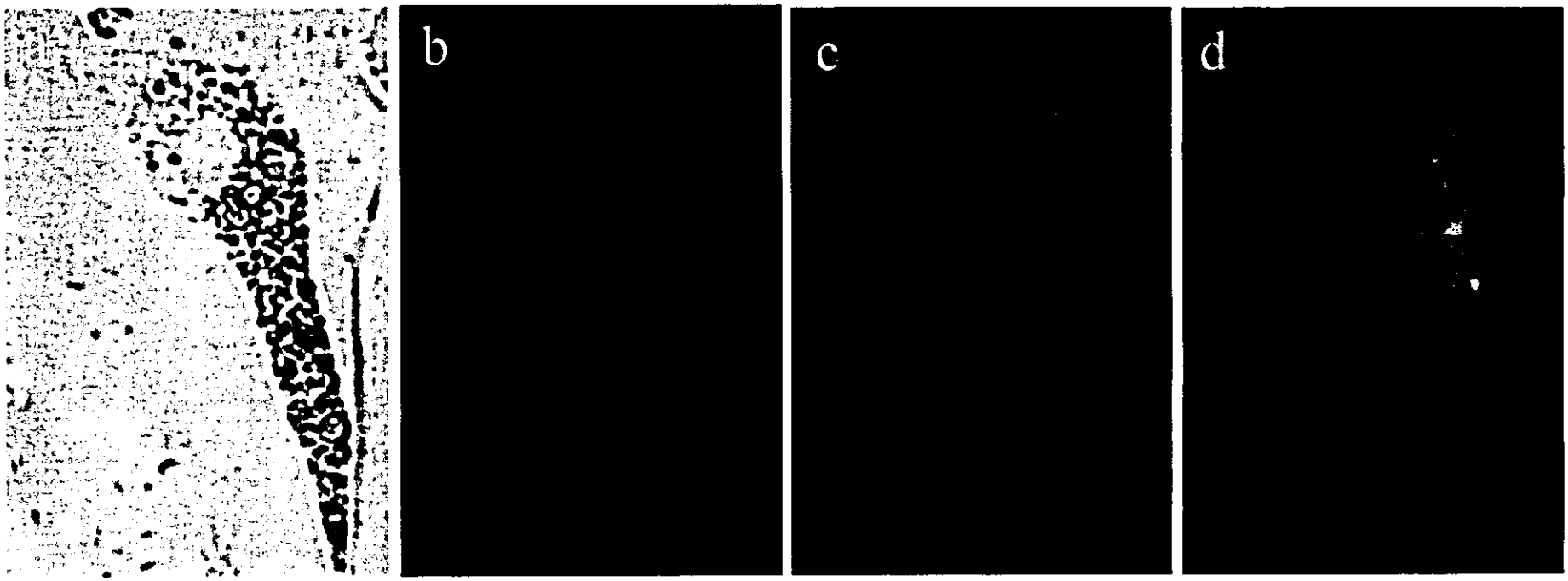

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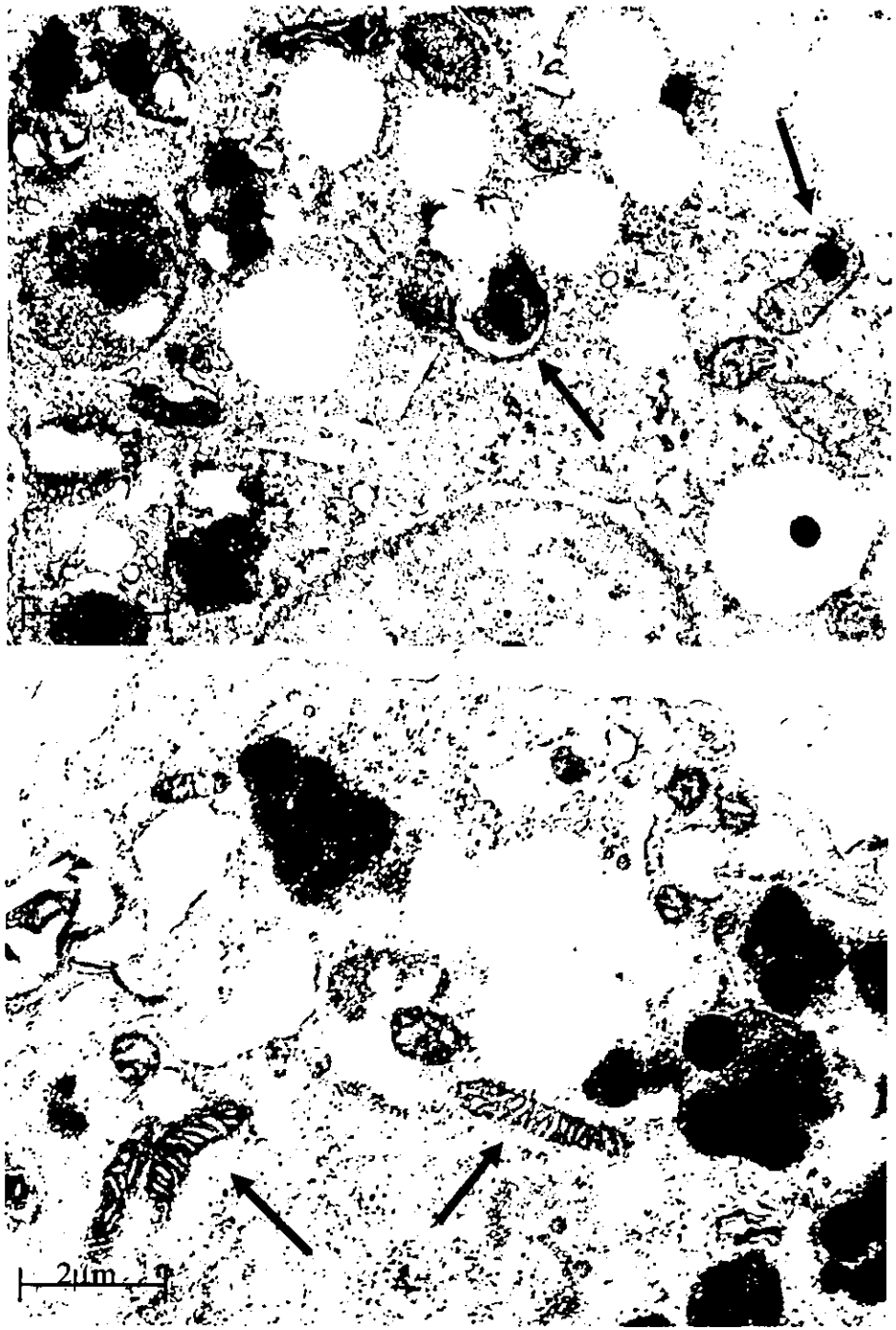

a

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Figure 7. Kosei Ijiri

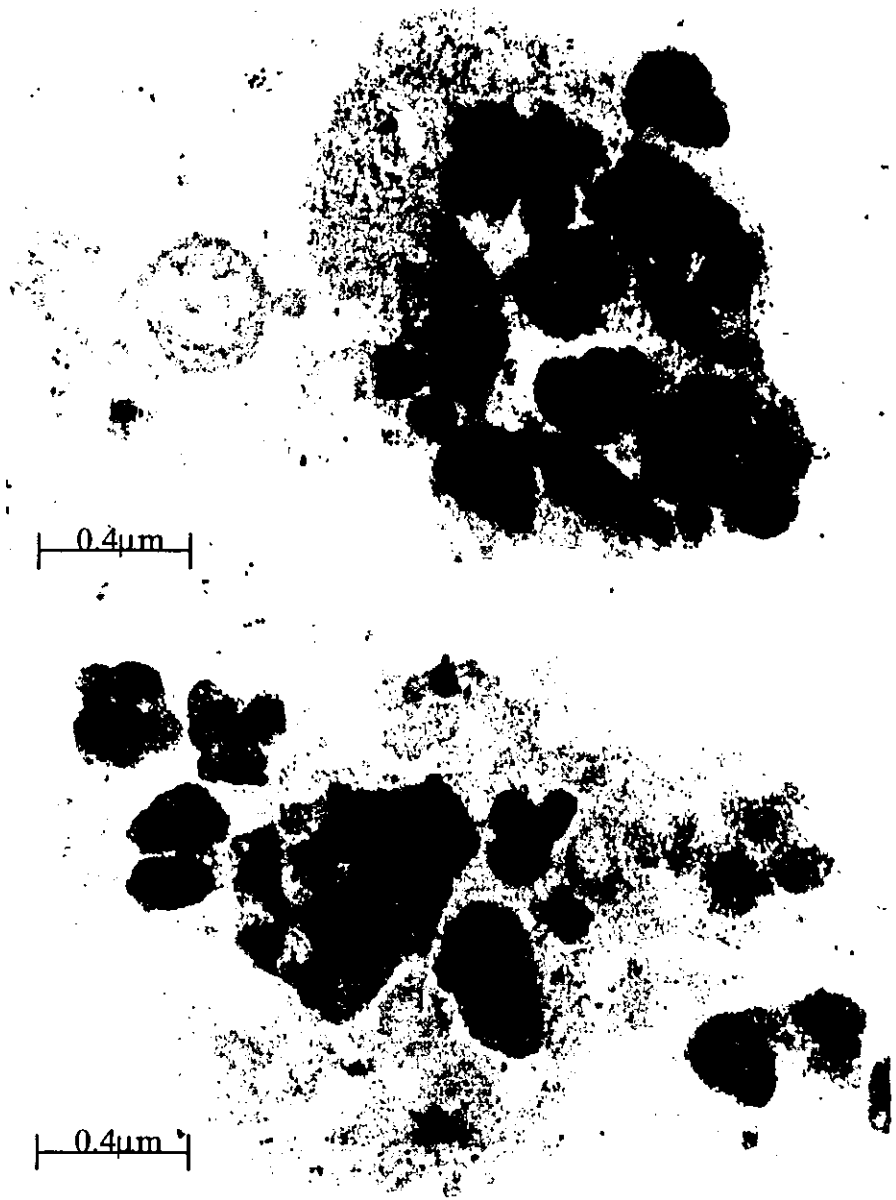

Figure 8. Kosei Ijiri

EARLY INTRAVENOUS GAMMA-GLOBULIN TREATMENT FOR KAWASAKI DISEASE: THE NATIONWIDE SURVEYS IN JAPAN

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Objective To determine the optimal period of intravenous gamma-globulin (IVGG) treatment, using the database from nationwide Kawasaki disease surveys in Japan.

Study design We selected patients who first visited a doctor within 3 days of illness and received IVGG treatment within 9 days of illness. We divided these patients into 2 groups: an early group (treated on days 1-4: 4731 cases) and a conventional group (days 5-9: 4020 cases). We compared the rate of additional IVGG and prevalence of cardiac sequelae between these groups.

Results The rate of additional IVGG in the early group was significantly higher than those of the conventional group (OR, 1.12 [95% CI, 1.10-1.16]). There were no significant differences in cardiac sequelae between the two groups.

Conclusions There is no evidence that IVGG treatment on day 4 or earlier has greater efficacy in preventing cardiac sequelae than treatment on days 5 to 9. In addition, early treatment is likely to result in a greater requirement for additional IVGG. However, there is also no evidence that early treatment increases the prevalence of cardiac sequelae in a clinical practice setting, where additional IVGG can be given to those whose initial treatment fails. *(J Pediatr 2004;144:496-9)*

The diagnosis of typical Kawasaki disease (KD) in Japan is based on at least 5 of the following 6 principal symptoms: (1) fever persisting for 5 or more days, (2) bilateral conjunctival congestion, (3) changes to the lips and oral cavity, (4) polymorphous exanthema, (5) changes to the peripheral extremities, and (6) acute nonpurulent cervical lymphadenopathy.

Atypical cases are defined as those with at least 4 of the symptoms listed above when coronary artery involvement was detected by echocardiography or coronary angiography. Suspected cases are defined as those who failed to fulfill the criteria listed above but in whom other diseases could be excluded. In the 16th nationwide survey in Japan, the ratio of patients who were treated with intravenous gamma-globulin (IVGG) within 4 days of illness was 30.5%.[1] However, it is controversial whether early IVGG treatment is beneficial or not.[2-6] Some reports suggest that early treatment with IVGG increases coronary artery complications.[4-6] The aim of this study was to determine the optimal period of initial IVGG treatment by using the database from nationwide surveys in Japan.

METHODS

The Japan KD Research Committee has conducted nationwide surveys since 1970.[7] The participants of these surveys are patients with KD who were diagnosed at hospitals with 100 beds or more. A questionnaire form is sent to the hospitals, with a pamphlet describing the diagnostic criteria of the disease and including color pictures of typical lesions of the skin, eyes, hands, and feet.[7] We used the database of the 15th (from 1997 to 1998) and 16th (from 1999 to 2000) nationwide surveys. The total number of patients in these surveys was 28,280 (12,966 in the 15th and 15,314 in the 16th).

IVGG	Intravenous gamma-globulin	KD	Kawasaki disease

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Supported in part by Grants-in-Aid 14570786 and 14770379 from the Ministry of Education, Culture, Sports, Science, and Technology, the Japanese Kawasaki Disease Research Committee, and the Mother and Child Health Foundation of Japan.

Submitted for publication Apr 11, 2003; last revision received Nov 6, 2003; accepted Dec 24, 2003.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2003.12.033

Table I. Characteristics of study patients

Variable	Initial day of treatment: Early (n = 4731)	Conventional (n = 4020)	P value
Age (mo)			
Mean ± SD	23 ± 20	29 ± 26	< .001*
Range	0.6-166	1-255	
Sex			
Male	2831 (60%)	2338 (58%)	
Female	1900 (40%)	1682 (42%)	.1†
Diagnosis			
Typical	4015 (85%)	3502 (87%)	
Atypical	197 (4%)	169 (4%)	.002†
Suspected	519 (11%)	349 (9%)	
Illness day of initial treatment (d)			
Mean ± SD	3.4 ± 0.7	5.6 ± 0.9	< .001*
Range	1-4	5-9	
IVGG dose per day (mg/kg)			
Mean ± SD	678 ± 516	664 ± 514	0.2*
Range	90-2222	100-2250	
Total IVGG dose in initial treatment (mg/kg)			
Mean ± SD	1720 ± 606	1681 ± 566	.002*
Range	400-4000	400-4000	

*P value determined by paired *t* test.
†P value determined by χ^2 test.

From these databases, we selected patients who first visited a doctor within 3 days of illness and received IVGG treatment within 9 days of illness. In these databases, the first day of fever was defined as day 1. We divided these patients into 2 groups: an early treatment group (treated with IVGG at 1-4 days of illness, 4731 cases) and a conventional treatment group (treated with IVGG at 5-9 days of illness, 4020 cases). The following data were obtained: age, sex, doses and period of IVGG treatment, additional IVGG treatment, acute cardiac lesions, and cardiac sequelae. Other data (such as the severity of inflammation) were not obtained in the nationwide surveys.

Acute cardiac lesions and cardiac sequelae were defined in the survey as the presence of one of the following within or after one month after onset: coronary artery aneurysms, coronary stenosis, myocardial infarction, and valvular lesions. Coronary artery aneurysm was defined by the Japanese Ministry of Health criteria for coronary artery abnormality in KD.[8] These criteria, applicable to either angiographic or echocardiographic measurement, classify coronary arteries as abnormal if the internal lumen diameter is greater than 3.0 mm in children younger than 5 years of age or greater than 4.0 mm in children at least 5 years of age; if the internal diameter of a segment measures at least 1.5 times that of an adjacent segment, or if the coronary artery lumen is clearly irregular.[8]

Table II. Univariate association between additional IVGG treatment and patient characteristics

	Additional IVGG treatment: −	+	P value
Sex			
Male	4485 (87%)	684 (13%)	.1
Female	3150 (88%)	432 (22%)	
Diagnosis			
Typical + atypical	6822 (87%)	1061 (13%)	< .001
Suspected	813 (94%)	55 (6%)	
Total IVGG dose in initial treatment (mg/kg)	1688 ± 552	1800 ± 784	< .001
Age (mo)	26 ± 23	25 ± 23	.4

For each factor observed, an odds ratio and 95% confidence interval were estimated by means of a multivariate logistic model. A 95% CI that did not include 1.0 was interpreted to indicate statistical significance. Analyses were performed with the use of SAS statistical software package (SAS Institute Inc, Cary, NC). We also analyzed the data excluding the suspected cases, since there is a possibility that patients with other diseases may have been inadvertently included in this group of patients.

RESULTS

The characteristics of these groups are shown in Table I. There were no significant differences between the two groups in sex and IVGG dose per day. The early treatment group was significantly younger than the conventional treatment group ($P < .001$). The ratio of suspected cases in the early treatment group was significantly higher than that in the conventional group ($P = .002$). The total IVGG dose in initial treatment in the early treatment group was significantly higher than that of in the conventional group ($P = .002$). The following regimens were frequently used in this study: 200 mg/kg for 5 days (7% of patients), 400 mg/kg for 5 days (51%), 1000 mg/kg for 1 day (11%), 1000 mg/kg for 2 days (14%), and 2000 mg/kg for 1 day (12%).

Univariate analysis showed that diagnosis ($P < .001$) and total IVGG dose in initial treatment ($P < .001$) were statistically significant predictors of additional IVGG (Tables II-IV). Sex ($P < .001$), diagnosis ($P < .001$), total IVGG dose in initial treatment ($P < .001$), and age ($P = .03$) were statistically significant predictors of acute cardiac lesions. Sex ($P < .001$), diagnosis ($P < .001$), and the total IVGG dose in initial treatment ($P = .04$) were statistically significant predictors of cardiac sequelae.

We compared the rate of additional IVGG treatment (Table V). The rate of additional IVGG treatment in the early treatment group was significantly higher than that in the conventional group (OR, 1.12 [95% CI, 1.10-1.16]). In the

Table III. Univariate association between acute cardiac abnormality and patient characteristics

	Acute cardiac abnormality		
	−	+	*P* value
Sex			
Male	3925 (76%)	1244 (24%)	< .001
Female	2942 (82%)	640 (18%)	
Diagnosis			
Typical + atypical	6068 (77%)	1815 (23%)	< .001
Suspected	799 (92%)	69 (8%)	
Total IVGG dose in initial treatment (mg/kg)	1689 ± 559	1752 ± 681	< .001
Age (mo)	25 ± 23	27 ± 25	.03

Table IV. Univariate association between cardiac sequelae and patient characteristics

	Cardiac sequelae		
	−	+	*P* value
Sex			
Male	4727 (91%)	442 (9%)	< .001
Female	3371 (94%)	211 (6%)	
Diagnosis			
Typical + atypical	7253 (92%)	630 (8%)	< .001
Suspected	845 (97%)	23 (3%)	
Total IVGG dose in initial treatment (mg/kg)	1698 ± 574	1759 ± 741	.04
Age (mo)	26 ± 23	25 ± 26	.6

Table V. Logistic analysis of additional IVGG treatment and cardiac outcome

Outcome	Early treatment (n = 4731)	Conventional treatment (n = 4020)	OR (95% CI)	Adjusted OR (95% CI)
Additional IVGG treatment	742 (16%)	374 (9%)	1.12 (1.10-1.16)	1.12 (1.10-1.16)
Acute cardiac abnormality	1046 (22%)	838 (21%)	1.01 (0.99-1.03)	1.02 (1.00-1.04)
Cardiac sequelae	370 (8%)	283 (7%)	1.02 (1.00-1.05)	1.02 (0.99-1.05)

Odds ratios have been adjusted for age, sex, diagnosis, and total IVGG dose in initial treatment.

subanalysis excluding the suspected cases, the result was similar (OR, 1.58 [95% CI, 1.40-1.78]).

We also compared the prevalence of acute cardiac lesions. The crude OR of acute cardiac lesions did not differ between the two groups (OR, 1.01 [95% CI, 0.99-1.03]). The adjusted OR also did not differ between the two groups (OR, 1.02 [95% CI, 1.00-1.04]). In the subanalysis, the adjusted OR also did not differ between the two groups (OR, 1.10 [95% CI, 0.99-1.22]).

Finally, we compared the prevalence of cardiac sequelae. The crude OR of cardiac sequelae did not differ between the two groups (OR, 1.02 [95% CI, 1.00-1.05]). The adjusted OR also did not differ between the two groups (OR, 1.02 [95% CI, 0.99-1.05]). In the subanalysis, the result was similar (OR, 1.11 [95% CI, 0.94-1.31]).

DISCUSSION

In this study, we investigated the optimal period of IVGG treatment. According to the US criteria, patients cannot be diagnosed before 5 days after onset.[9] However, in the presence of classic features, the diagnosis of KD may be made by experienced observers before day 5 of fever. There were no significant differences in acute cardiac abnormalities and cardiac sequelae between the early treatment group and the conventional treatment group. According to a case-control study by Sugahara et al,[3] the rate of additional IVGG treatment and prevalence of cardiac sequelae in the early and conventional treatment groups were similar, but total duration of fever in the early treatment group was significantly shorter than that in the conventional group.

However, in this study, the rate of additional IVGG in the early treatment group was significantly higher than that in the conventional treatment group. Han et al[10] also reported that children who received additional treatment had a significantly lower median number of days from fever onset to the initial course of IVGG. However, the odds ratio of additional treatment is very low, at 1.12; therefore, the effect size is very small. Unfortunately, we could not perform multivariate analysis because of limited data about other risk factors (such as white blood cell count, C-reactive protein) associated with the need for IVGG retreatment. It is possible that no significant effect would be found whether early IVGG treatment is provided or not.

This result might be because children treated before day 5 (and who therefore did not meet the criteria for KD) had a viral syndrome or a different illness that did not respond to IVGG and therefore required additional treatment. Or, it might be that additional IVGG decreased the prevalence of cardiac sequelae, so the prevalence of cardiac sequelae in the two groups was similar. One potential problem is that the criteria for the early treatment group were not consistent with

the requirement of 5 days of fever. In addition, suspected cases with cardiac involvement as well as with fatal outcome that did not meet the diagnostic criteria have been reported.[11,12] Therefore, we analyzed all the cases. However, to settle this question, we conducted a subanalysis that excluded the suspected cases. The subanalysis could exclude the patients with other illnesses. The results of subanalysis were similar. As a result of this subanalysis, we believe that the latter hypothesis is true.

Tse et al[2] reported that early treatment of KD resulted in shorter total fever duration and less cardiac sequelae and that there was no association between early treatment and increased treatment failures, length of hospitalization, or development of cardiac sequelae. Our results are difficult to compare with those of the Tse publication, due to a different method of counting illness days. In the Tse publication, the first day of illness was counted as the day after onset of fever rather than as the first day of fever. However, at the very least, early treatment did not increase the cardiac sequelae.

The total dose in initial IVGG treatment in the early treatment group was significantly greater than that in the conventional group. Our hypothesis is that because the early treatment group contained younger and more severe cases who were therefore treated with a greater dose of IVGG in initial treatment. In Japan, the Harada score is frequently used to determine severity.[13] Some institutions determine the dose of IVGG by using the Harada score. However, the difference of total dose was very small, and therefore the effect of the difference may not be clinically significant.

Finally, there are several limitations in this study. The retrospective study design did not allow determination of the risk of cardiac complications. In addition, the information that could be obtained was limited. We could not control differences in treatment (use of such agents as aspirin and steroids) between institutions and by the severity of the illness. This problem is very important, and we will consider questions about aspirin (whether to use it or not, dose) and other drugs in the next survey. The definition of coronary artery involvement in this study is also important. de Zorzi et al[14] reported that the use of Japanese Ministry of Health criteria might underestimate the true incidence of coronary artery dilation in patients with KD.

There is no evidence that treatment with IVGG on day 4 or earlier has greater efficacy in preventing cardiac sequelae than treatment on days 5 through 9. In addition, early treatment results in a greater requirement for additional IVGG treatment. However, there is also no evidence that early IVGG treatment increases the prevalence of cardiac sequelae in a clinical practice setting where additional IVGG treatment can be given to those in whom the initial IVGG treatment fails.

REFERENCES

1. Yanagawa H, Nakamura Y, Yashiro M. The results of 16th nationwide survey of Kawasaki disease in Japan. J Pediatr Practice 2002;65:332-42 (in Japanese).
2. Tse SML, Silverman ED, McCrindle BW, Yeung RSM. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease. J Pediatr 2002;140:450-5.
3. Sugahara Y, Ishii M, Muta H, Furui J, Himeno W, Akagi T, et al. The effectiveness and safety of early intravenous immune globulin treatment for Kawasaki disease. Presented at the 7th International Kawasaki Disease Symposium. Hakone. December 7, 2001. Report.
4. Ogino H, Kiyosawa N, Nishioka K, Onouchi Z, Kamiya T, Furusho K, et al. Questionnaire survey on gamma-globulin therapy for Kawasaki disease in the Kinki district. Prog Med 1996;16:1817-25 (in Japanese).
5. Ito H, Kiyosawa N, Ogino H, Nakamura Y, Yanagawa H. The relationship between the initial day of gamma-globulin treatment in Kawasaki disease and cardiac sequelae. Prog Med 2001;21:1608-12 (in Japanese).
6. Yanagawa H, Nakamura Y, Sakata K, Yashiro M. Use of intravenous gamma-globulin for Kawasaki disease: effect on cardiac sequelae. Pediatr Cardiol 1997;18:19-23.
7. Yanagawa H, Nakamura Y, Yashiro M, Oki I, Hirata S, Zhang T, et al. Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. Pediatrics 2001;107. URL: http://www.pediatrics.org/cgi/content/full/107/3/e33.
8. Research Committee on Kawasaki diseases. Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Tokyo, Japan: Ministry of Health and Welfare; 1984.
9. Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, et al. Diagnosis and therapy of Kawasaki disease. Circulation 1993;87:1776-81.
10. Han RK, Silverman ED, Newman A, McCrindle BW. Management and outcome of persistent or recurrent fever after initial intravenous gamma globulin therapy in acute Kawasaki disease. Arch Pediatr Adolesc Med 2000;154:694-9.
11. Rowley AH, Gonzalez-Crussi F, Gidding SS, Duffy CE, Shulman ST. Incomplete Kawasaki disease with coronary artery involvement. J Pediatr 1987;110:409-13.
12. Loubser MD, Hoh MC, Sreeram N. Sudden death in incomplete Kawasaki disease. Arch Dis Child 1989;64:637-8.
13. Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. Acta Paediatr Jpn 1991;33:805-10.
14. de Zorzi A, Colan SD, Gauvreau K, Baker AL, Sundel RP, Newburger JW. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. J Pediatr 1998;133:254-8.

Older Age Is a Risk Factor for the Development of Cardiovascular Sequelae in Kawasaki Disease

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ABSTRACT. *Objectives.* To clarify the characteristics of Kawasaki disease (KD) in children 6 years and older and to determine whether age is a risk factor for cardiovascular abnormalities.

Methods. Patients who had KD and were reported between 1999 and 2000 in the 16th nationwide survey of KD in Japan (n = 15 314) were analyzed. Patients who were aged 6 years or older (older group) were matched with patients who were aged 6 months to 3 years and were treated at the same hospital (younger groups). The total number of analyzed patients was 1498 (749 matched pairs).

Results. The proportion of complete KD in the older group was similar to that in the younger group. Recurrent cases in the older group were significantly more common than those in the younger group (9% vs 2%). The proportion of patients who were treated with intravenous γ-globulin in the older group was significantly lower than that in the younger group (82% vs 87%). The proportion of older group patients who were treated with intravenous γ-globulin at or after 7 days of illness was significantly higher than that in the younger group (35% vs 14%). There was a higher prevalence of cardiovascular abnormalities in the older group than in the younger group (20% vs 15%). Multivariate logistic regression analysis showed that older age was an independent risk factor for cardiovascular sequelae (odds ratio: 1.58; 95% confidence interval: 1.01–2.46).

Conclusions. In children older than 6 years, age is an independent risk factor for cardiovascular sequelae in KD. *Pediatrics* 2004;114:751–754; *Kawasaki disease, cardiovascular sequelae, older children, intravenous γ-globulin.*

ABBREVIATIONS. KD, Kawasaki disease; IVGG, intravenous γ-globulin; OR, odds ratio; CI, confidence interval.

Kawasaki disease (KD) is an acute febrile illness of unknown cause.[1] Several epidemiologic studies have revealed that KD usually affects children younger than 3 years and is more common in boys.[2,3] It is widely known that male gender and age <12 months are independent risk factors for cardiovascular sequelae.[4] Our clinical impression was that KD in older children is uncommon but can contribute to cardiovascular sequelae. There have been a few descriptions of KD in older children.[5,6] In these studies, older patients had a greater occurrence of additional symptoms and cardiovascular sequelae; however, the symptoms were less commonly associated with KD.[5,6] It was not clear, however, whether older age was an independent risk factor for cardiovascular sequelae because too few patients had been studied. In the present study, we attempted to identify the clinical features and outcomes of KD in children 6 years and older.

METHODS

Nationwide surveys of KD in Japan are conducted every 2 years.[2] Participants in the surveys are patients whose KD was diagnosed at hospitals with 100 beds or more. In the most recent survey (the 16th, covering a 2-year period starting January 1, 1999, and ending December 31, 2000), 2619 hospitals participated. A questionnaire was sent to pediatricians along with a pamphlet describing the diagnostic criteria for the disease. The pamphlet included color pictures of typical lesions on the skin, eyes, hands, and feet. Pediatricians completed it. The total number of patients in the survey was 15 314.

Patients with KD were divided into 2 groups according to the diagnostic criteria. Diagnosis of complete KD in this survey was based on a patient's exhibiting at least 5 of the following 6 principal symptoms: 1) fever persisting for 5 or more days, 2) bilateral conjunctival congestion, 3) changes to the lips and oral cavity, 4) polymorphous exanthema, 5) changes to the peripheral extremities, and 6) acute nonpurulent cervical lymphadenopathy. Diagnosis of incomplete cases was defined as those with 4 or fewer of the symptoms listed above, with or without cardiovascular abnormalities.

Cardiovascular abnormalities were divided into 2 categories according to the duration of their conditions: 1) transient dilation, defined as a coronary artery dilation or aneurysm existing in an acute stage but showing no cardiovascular lesions within 1 month of onset, and 2) cardiovascular sequelae, defined as 1 of the following symptoms appearing 1 month after onset: coronary artery aneurysms, coronary stenosis, myocardial infarction, and valvular lesions. Criteria for defining a coronary artery aneurysm or artery abnormality in KD were defined by the Japanese Ministry of Health.[7] These criteria, applicable to either angiographic or echocardiographic measurements, classify coronary arteries as abnormal when 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 measures at least 1.5 times that of an adjacent segment, or when the coronary artery lumen is clearly irregular. A giant aneurysm was defined as the internal lumen diameter being >8 mm.

The following data were obtained: age, gender, diagnostic categories, family history, recurrence, the use of intravenous γ-globulin (IVGG) treatment, additional IVGG treatment, and cardiovas-

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Accepted for publication Dec 23, 2003.
DOI: 10.1542/peds.2003-0118-F

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cular sequelae. Other data (eg, severity of inflammation) were not obtained in the nationwide surveys.

From this database, we selected all patients who were 6 years of age or older at the time of illness. We selected the matched-pair younger cases only when the patient met the following criteria: same gender, 3 months to 3 years of age at the time of illness, and treated at the same hospital in the same calendar year. A total of 805 cases (5.3% of total reported cases) were reported as older cases. Among the 805 cases, 56 were excluded because appropriate younger cases did not exist. Therefore, a total of 749 older and 749 younger cases were studied.

Nominal data were analyzed using the χ^2 test. Continuous variables were compared using the t test. $P < .05$ was considered statistically significant. The odds ratio (OR) with 95% confidence interval (CI) for the cardiovascular abnormalities was calculated by using Cox regression analysis after adjusting for gender, diagnostic categories, first day of IVGG treatment after onset, and total dose of IVGG therapy. Analyses were performed using SPSS 11.0 (SPSS Inc, Chicago, IL).

RESULTS

Profiles

The proportion of complete KD in the older group was similar to that in the younger group, as were sibling and patient histories. Recurrent cases (a second or more episode of the disease separate from the first) in the older group were significantly more common than in the younger group (9% vs 2%). The proportion of older children who first visited a doctor within 7 days of illness onset was significantly lower than that of the younger group (84% vs 91%; Table 1).

IVGG Treatment

The proportion of patients who were treated with IVGG in the older group was significantly lower than that in the younger group (82% vs 87%). In patients who were not treated with IVGG, the proportion of complete KD patients in the older group was significantly higher than that in the younger group (54% vs 42%; $P < .001$). However, the complication rate of transient dilation (7% vs 7%; $P = .94$) and cardiovascular sequelae (4% vs 3%; $P = 1.0$) in the older group did not differ from those in the younger group. The complication rate of cardiovascular abnormalities in complete KD patients who were not treated with IVGG was lower than those who had complete KD and received initial IVGG treatment at a total dose of 2000 mg/kg within 9 days of illness onset (the dose and timing recommended by the American Heart Association[8]; 9% vs 18%; $P = .01$; Table 2).

The proportion of patients who were treated with IVGG at or after 7 days of illness was significantly higher than that in the younger group (35% vs 14%). In addition, there was a tendency for fewer patients in the older group to be treated with single administration of high-dose IVGG than those in the younger group. Regarding IVGG retreatment, there was no significant difference between the 2 groups.

Cardiovascular Abnormalities

There was a higher prevalence of cardiovascular abnormalities in the older group than in the younger group. The complication rate of transient dilation in complete KD was lower than that in incomplete KD (12% vs 16%; $P = .02$). The complication rate of cardiovascular sequelae in complete KD did not differ than that in incomplete KD (6% vs 8%; $P = .2$; Table 3).

To determine whether age >6 years was an independent risk factor for the development of cardiovascular abnormalities, we performed conditional logistic regression analysis after adjusting for other confounding variables. The confounding variables were determined by the results of univariate analysis. Multivariate logistic regression analysis showed

TABLE 1. Characteristics of Studied Patients

	Older Group (n = 749)	Younger Group (n = 749)	
Gender (male:female)	422:327	422:327	matched
Diagnosis			
Complete KD	601 (80%)	602 (80%)	
Incomplete KD	148 (20%)	149 (20%)	
Sibling history	15 (2%)	8 (1%)*	
Parents' history	0 (0%)	2 (0.3%)	
Recurrence	69 (9%)	15 (2%)*	
Day of first hospital visit after onset	4.6 ± 2.4	4.3 ± 2.1*	
Day 1–3	259 (35%)	280 (37%)	
Day 4–6	370 (49%)	403 (54%)	
Day 7–9	97 (13%)	50 (7%)	*
Day 10–	22 (3%)	14 (2%)	
Unknown	1 (0.1%)	2 (0.3%)	

* $P < .05$.

TABLE 2. IVGG Treatment

	Older Group (n = 749)	Younger Group (n = 749)	
IVGG treatment	612 (82%)	654 (87%)*	
Day IVGG given after onset	4.9 ± 3.1	4.5 ± 2.6*	
Day 1–3	32 (5%)	77 (12%)	
Day 4–6	363 (59%)	476 (73%)	
Day 7–9	184 (30%)	74 (11%)	*
Day 10–	28 (5%)	21 (3%)	
Unknown	5 (1%)	6 (1%)	
Dosing regimens of initial IVGG			
200 mg/kg for 5 d	69 (11%)	55 (8%)	
400 mg/kg for 5 d	277 (45%)	284 (44%)	
1000 mg/kg for 1 d	75 (12%)	74 (12%)	
1000 mg/kg for 2 d	114 (17%)	139 (21%)	
2000 mg/kg for 1 d	63 (10%)	89 (14%)	
Other regimens	14 (2%)	13 (2%)	
Total dose of initial IVGG			
<900	33 (5%)	30 (5%)	
901–1500	164 (27%)	146 (22%)	
1501<	415 (68%)	478 (73%)	
IVGG retreatment	61 (8%)	67 (9%)	

* $P < .05$.

TABLE 3. Cardiovascular Abnormalities

	Older Group (n = 749)	Younger Group (n = 749)
Total	153 (20%)	113 (15%)*
Giant aneurysm	7 (0.9%)	1 (0.1%)
Aneurysm	20 (3%)	10 (1%)
Dilation	30 (4%)	25 (3%)
Transient dilation	96 (13%)	77 (10%)
Stenosis	1 (0.1%)	0
Myocardial infarction	1 (0.1%)	0
Valvular lesion	5 (0.7%)	4 (0.5%)

* $P < .05$.

TABLE 4. Multivariate Logistic Regression Analysis of Cardiovascular Abnormalities

	Older Group	Younger Group	Adjusted OR* (95% CI)
Transient dilation	96 (13%)	77 (10%)	1.37 (1.03–1.82)
Cardiovascular sequelae	57 (8%)	36 (5%)	1.58 (1.01–2.46)

* ORs were adjusted for gender, diagnosis, first day of IVGG treatment after onset, and the total IVGG dose in initial treatment.

that age >6 years was an independent risk factor for transient dilation (OR: 1.37; 95% CI: 1.03–1.82) and cardiovascular sequelae (OR: 1.58; 95% CI: 1.01–2.46; Table 4).

Finally, to control for the other confounding variables such as total dose and timing of IVGG, we analyzed only the complete KD patients who received initial IVGG treatment at a total dose of 2000 mg/kg within 9 days of illness onset. The total number of analyzed patients was 618 (286 older and 332 younger cases). There were also higher prevalences of transient dilation (13% vs 11%) and cardiovascular sequelae (9% vs 3%) in the older group. The ORs with 95% CIs for the transient dilation and cardiovascular sequelae were 1.59 (1.04–2.45) and 3.11 (1.46–6.60), respectively.

DISCUSSION

In this study, we observed a delay in IVGG treatment and a higher incidence of cardiovascular abnormalities in older children (6 years and older).

Clinical Features

Using the Japanese criteria for KD, there were no significant differences observed in the diagnostic categories between the 2 groups. However, the proportion of older group patients who first visited a doctor within 7 days of illness onset was significantly lower than that of the younger group. This result means that the older patients were delayed in being referred to a hospital for treatment. Momenah et al[5] noted that the time interval for diagnosing in older children was more than twice that for the more typical age group. Unfortunately, we did not investigate the date of diagnosis, so we have no data regarding the time interval. However, in the cases with IVGG treatment, the date of diagnosis was nearly equal to the IVGG treatment starting date. In this study, the proportion of patients in the older group who were treated with IVGG after 7 days of illness was significantly higher than that of the younger group. We might conclude, therefore, that the diagnosis date for the older group was significantly later than that for the younger group.

Sibling and patient histories did not differ in the 2 groups. As such, we can speculate that there was no relationship between the age of KD onset and genetic factors. It was not surprising that the number of recurrent cases in the older group was higher than in the younger group, because the older group had more time to be affected by KD.

IVGG Treatment

The older KD patients in Japan tended to be treated at a later stage of disease and with less IVGG treatment. The older groups also tended not to receive IVGG treatment. We could not determine the treatment regimens for such patients. It may have been aspirin alone or no diagnosis before fever defervescence.

In patients who were not treated with IVGG, the proportion of complete KD patients in the older group was significantly higher than that in the younger group. In addition, the complication rate of cardiovascular abnormalities in the older group did not differ from that in the younger group. This result might mean that KD in older children is more difficult to diagnose and therefore children miss their chance of IVGG treatment.

It is interesting that the complication rate of cardiovascular abnormalities in complete KD patients who were not treated with IVGG was lower than that of patients who had complete KD and received recommended IVGG treatment. There are 2 possible explanations. First, approximately half of the patients who were not treated with IVGG in each group had incomplete KD; therefore, some of these patients might not have had KD at all. Second, patients who were not treated with IVGG were believed to be at low risk for the development of cardiovascular abnormalities and therefore did not receive IVGG. However, in patients who were not treated with IVGG, the complication rate of cardiovascular sequelae in the complete KD did not differ from that in incomplete KD (2% vs 5%; $P = .5$). Therefore, we believe that the latter hypothesis is true. Compared with the United States, in which almost all patients with KD or suspected KD receive IVGG, Harada's score is frequently used for the selection of IVGG treatment in Japan.[4,9]

Cardiovascular Sequelae

In this study, we found a higher prevalence of cardiovascular sequelae in the older group. Multivariate logistic regression analysis showed that older age was an independent risk factor for transient dilation and cardiovascular sequelae. In addition, there was a higher prevalence of cardiovascular abnormalities in the older group who had complete KD and received recommended IVGG treatment. This result means that even when the older group receives adequate treatment, the risk of cardiovascular abnormalities is higher. Stockheim et al[6] noted that older age at the onset of illness might be an independent risk factor. This study supports such previous findings.

Clinical Implications

Older children with KD tend to have a delayed diagnosis. The primary pediatrician, therefore,

should consider KD in cases in which older children have prolonged fever or other KD-like symptoms. In addition, older age should be recognized as an independent risk factor for the development of cardiovascular sequelae, and high-dose IVGG treatment should begin as soon as possible. Harada's score would be useful for the selection of IVGG treatment in older patients. It may also be necessary to formulate a new strategy for older KD patients.

Limitations

In the present study, we did not collect the following data: the presence of 6 major symptoms, other clinical features, the date of diagnosis, or laboratory data. Therefore, we did not compare the presence of individual symptoms. The study was limited by its retrospective design, so we could not conclude an accurate risk for cardiovascular abnormalities. In addition, we did not control the treatment regimens for KD at the various institutions, and we could not compare the precise risk of cardiovascular abnormalities because we could not control for the severity of the inflammation. The diagnostic methods of cardiovascular abnormalities might be biased. Despite these limitations, the sample size was large enough to permit the following conclusions to be made.

CONCLUSIONS

Older children with KD experience a delay in both diagnosis and treatment with IVGG. In addition, in children older than 6 years, age is an independent risk factor for the development of cardiovascular sequelae.

ACKNOWLEDGMENT

This work was supported in part by Grants-in-Aid 14570786 and 14770379 from the Ministry of Education, Science and Culture of Japan.

REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children [in Japanese]. *Arerugi.* 1967;16:178–222
2. Yanagawa H, Nakamura Y, Yashiro M, et al. Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. *Pediatrics.* 2001;107(3). Available at: www.pediatrics.org/cgi/content/full/107/3/e33
3. Morens DM, Anderson LJ, Hurwitz ES. National surveillance of Kawasaki disease. *Pediatrics.* 1980;65:21–25
4. Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. *Acta Pediatr Jpn.* 1991;33:805–810
5. Momenah T, Sanatani S, Potts J, Sandor GGS, Human DG, Patterson MWH. Kawasaki disease in the older child. *Pediatrics.* 1998;102(1). Available at: www.pediatrics.org/cgi/content/full/102/1/e7
6. Stockheim JA, Innocentini N, Shulman ST. Kawasaki disease in older children and adolescents. *J Pediatr.* 2000;137:250–252
7. Research Committee on Kawasaki Disease. *Report of Subcommittee on Standardization of Diagnostic Criteria and Reporting of Coronary Artery Lesions in Kawasaki Disease.* Tokyo, Japan: Ministry of Health and Welfare; 1984
8. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation.* 1993;87:1633–1639
9. Witt TM, Minich LL, Bohnsack JF, Young PC. Kawasaki disease: more patients are being diagnosed who do not meet American Heart Association criteria. *Pediatrics.* 1999;104(1). Available at: www.pediatrics.org/cgi/content/full/104/1/e10

A CONVERSATION WITH ROBERT C. RICHARDSON, NOBEL LAUREATE 1996: THE CHILLING OF AMERICAN SCIENCE

"Dr Richardson, now 66 and a professor at Cornell, has used the prestige of his Nobel to campaign for improved science education. And he lives his beliefs; he is one of the few science laureates teaching undergraduate classes. . . . We have to face facts. We've got a serious scientific manpower problem, and it's been developing since the 1970's. We used to be third in the world, behind Japan and Finland, in the percentage of our students who became scientists and engineers. Now we are 23rd. For 30 years, we've made do by importing a large portion of our scientists. Smart, motivated people from places like China and India studied and settled in the United States. Today, about half of our graduating engineers are foreign-born."

Dreifus C. *New York Times.* July 6, 2004

Noted by JFL, MD

Older Age Is a Risk Factor for the Development of Cardiovascular Sequelae in Kawasaki Disease

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Pediatrics 2004;114;751-754
DOI: 10.1542/peds.2003-0118-F