Table 2. Transmission of genetic variants in *CASP3* from European American parents to their offspring with Kawasaki disease

Variants	TDT Risk allele	RAF[a]	T:U[b]	OR	95% CI	*P*-value
rs13108061	–	0.44	114:114	1.00	0.77–1.30	1.00
rs2720382	T	0.83	78:54	1.44	1.02–2.04	0.037
rs2705883	C	0.69	120:80	1.50	1.13–1.99	4.7×10^{-3}
rs4862399	T	0.88	50:49	1.02	0.69–1.51	0.92
rs34605630	C	0.68	122:85	1.44	1.09–1.89	0.010
rs4861629	C	0.81	82:58	1.41	1.01–1.98	0.043
rs7699420	A	0.82	82:63	1.30	0.94–1.81	0.11
rs2705881	C	0.82	82:59	1.39	0.99–1.94	0.053
rs7693625	T	0.81	78:70	1.11	0.81–1.54	0.51
rs1405937	C	0.81	82:62	1.62	0.95–1.84	0.096
rs12108497	G	0.68	122:84	1.45	1.10–1.92	8.1×10^{-3}
Intergene_1	C	0.82	74:58	1.28	0.90–1.80	0.16
Intergene_2	C	0.72	112:78	1.44	1.08–1.92	0.014
rs72689236	A	0.70	120:79	1.54	1.16–2.05	3.7×10^{-3}
rs62339863	T	0.71	122:78	1.56	1.18–2.08	1.9×10^{-3}
casp3_4	G	0.66	134:95	1.41	1.08–1.83	0.010
rs2720379	C	0.68	121:82	1.48	1.11–1.95	6.2×10^{-3}
rs2720378	G	0.68	118:84	1.40	1.06–1.86	0.017
rs4647610	G	0.85	72:53	1.36	0.95–1.94	0.089
rs4647616	G	0.84	70:53	1.32	0.92–1.89	0.13
rs4647617	G	0.84	70:53	1.32	0.92–1.89	0.13
rs59760601	C	0.84	68:49	1.39	0.96–2.00	0.079
rs2720377	A	0.68	121:81	1.49	1.13–1.98	4.9×10^{-3}
rs4647652	C	0.87	58:50	1.16	0.79–1.69	0.44
rs4647655	del (TTCAG GATTT)	0.87	59:50	1.18	0.81–1.72	0.39

[a]Risk allele frequency.
[b]'T' and 'U' indicate transmitted and untransmitted risk alleles of each variant.

Puga *et al.* (18) described that caspase-3 induced by Nfatc2 leads to T cell anergy by downregulating TCR signaling. The transient T cell anergy in KD patients in acute and convalescent phases which have been documented in several reports (19–21) might be, at least partly, related to induction of caspase-3 in T cells by activated NFATc2. No apparent gene–gene interaction between *ITPKC* and *CASP3* was detected in the logistic regression analysis of the SNPs (rs28493229 in *ITPKC* and rs2720378 or rs72689236 in this study, data not shown). However, it is of great interest that NFAT is involved in both pathways in which these SNPs have a functional role (Supplementary Material, Fig. S5). It has also been reported that Nfatc2 is a substrate for caspase-3 (22). It may be that the induction of caspase-3 acts as a negative feedback mechanism to regulate activation of the Ca^{2+}/NFAT pathway. There are likely to be several molecular networks playing major roles in the pathogenesis of KD. Our present findings further highlight the Ca^{2+}/NFAT pathway as a main axis in regulating these networks. Since many inhibitors of this pathway such as cyclosporine and tacrolimus are in clinical use, further elucidation of the role of caspase-3 in the pathophysiology of KD may lead to new preventive and therapeutic strategies for this vasculitis.

MATERIALS AND METHODS

DNA samples

We recruited 920 Japanese KD patients from several medical institutes in Japan. All Japanese KD patients (male:female:no info = 554:365:1) were diagnosed by pediatricians according to the Japanese criteria (23). Median age of disease onset was 23.0 months (range 1–136). Healthy Japanese adults without a history of KD ($n = 1409$) were also recruited as controls from several medical institutes. DNA samples from 249 KD subjects of European descent (male:female = 163:86) and their biological parents were collected by several medical institutes participating in the US KD Genetics Consortium. The study was approved by the ethical committee of RIKEN and the institutional review board of all participating institutions. Written informed consent and assent as appropriate were obtained from subjects and their parents.

Re-sequencing and genotyping

Data regarding tagging SNPs were obtained from the website of International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap24_B36/). LD map in Figure 1 was created using Haploview 4.1 software (http://www.broad.mit.edu/haploview/haploview). For SNP discovery, we resequenced the genomic region (NT_022792.17: from nt 17,956,305 to 17,992,719) using DNA from 12 KD patients and 12 controls. Repetitive sequences except for those in the region from the promoter to intron 1 of *CASP3* were excluded from the analysis. We genotyped SNPs and insertion/deletion polymorphisms using the Invader assay (24) and direct sequencing, respectively.

Statistic analysis

Association of the SNPs was analyzed using a chi-square test. Meta-analysis of data from case–control sets was conducted by Mantel–Haenszel methodology. Transmission disequilibrium test was performed using TDT software (25) integrated in Haploview 4.1. Haplotype analysis was conducted by using the program THESIAS (26) (http://genecanvas.ecgene.net/news.php) and conditional log-likelihood with Akaike information criterion (AIC): AIC = $-2 \times$ (the maximized value of the conditional log-likelihood) $+ 2 \times$ (the number of parameters). As the number of parameters, we used the number of alleles or haplotypes with frequencies >0.01 that were used for each model. In the logistic regression analysis of a SNP, we first applied a 1 degree-of-freedom (1 d.f.) likelihood ratio test to determine whether a 1 d.f. multiplicative allelic effects model or a 2 d.f. full genotype model was more appropriate (26). Because we did not find any significant difference from the full genotype model ($P > 0.05$), we assumed a multiplicative allelic effects mode. Next, we carried out a forward logistic regression analysis, where we started by assessing whether the most significant SNP was sufficient to model the association among the SNP set. For this, we used a 1 d.f. likelihood ratio test for adding each of the remaining SNPs to the model by assuming multiplicative allelic effects for the additional SNPs.

Luciferase assay

Jurkat E6-1 cells and HeLa cells were obtained from ATCC and the RIKEN Cell Bank, respectively. PBMCs from healthy volunteers were separated from venous blood using

Lymphoprep reagent (Axis-Shields). $CD3^+$ T cells were isolated using iMag system with a monoclonal antibody against human CD3 (clone HIT3a) conjugated with magnetic beads (BD Biosciences). We cloned single or four tandem copies of 31 nucleotides for each SNP region upstream of the SV40 promoter of the pGL3-promoter vector (Promega). The minimal promoter region of *CASP3* (nt −38 of 5′ flanking to +17 of intron 1) was cloned into pGL3-basic vector. These reporter plasmids were co-transfected with phRGTK vector into the cells. C-016 and O-005 programs of the Nucleofector (Amaxa) were used for transfection into Jurkat E6-1 and HeLa, respectively. Transfection into PBMCs and $CD3^+$ T cells was conducted with U-014 program. Twenty-four hours after transfection, Jurkat cells, PBMCs and $CD3^+$ T cells were stimulated with 1 μg/ml of ionomycin (SIGMA) and 50 ng/ml of PMA (SIGMA) for 4 h and harvested. Suppression of NFAT activity was performed by adding 100 ng/ml of cyclosporin A (CALBIOCHEM) in the above-mentioned stimulation medium. Luciferase activity was measured with the Dual Luciferase Reporter Assay system (Promega). We also cloned cDNAs of NFATc1 (NM_172390) and NFATc2 (NM_173091) into pcDNA3.1(+) (Invitrogen) and co-transfected with reporter vectors for rs72689236 to test the effect of overexpression of these proteins on enhancer activity.

Electorophoretic mobility shift assay

PBMCs were incubated in RPMI 1640 medium supplemented with 10% of fetal bovine serum and stimulated with ionomycin (1 μg/ml) and PMA (50 ng/ml) for 2 h. Suppression of NFAT activity was achieved by adding 100 ng/ml of cyclosporin A to the stimulation medium. After lysing the cells with buffer A [10 mM HEPES-KOH (pH 7.8), 10 mM KCl, 0.1 mM EDTA, 0.1% NP-40 and protease inhibitor cocktail], nuclear extracts were prepared using buffer C [50 mM HEPES-KOH (pH 7.8), 420 mM KCl, 0.1 mM EDTA, 5 mM $MgCl_2$, 2% glycerol and protease inhibitor cocktail]. Eighteen base pairs of double-stranded oligonucleotides corresponding to G and A alleles of rs72689236 were labeled with digoxygenin -11-ddUTP using DIG Gel Shift Kit (Roche). Probes were incubated with 5 μg of nuclear extract pre-incubated with 0.2 μg of poly d(I-C), 1 μg of poly-L-lysin for 30 min in room temperature. For the supershift assay, nuclear extract and monoclonal antibodies (Santa Cruz) or isotype control IgGs (R&D SYSTEMS) were incubated for 1 h on ice prior to the binding reaction. Competition was conducted with 100× molar excess of unlabeled oligonucleotides. Sequences of the oligonucleotides are provided in Supplementary Material, Table S4. The binding reaction mixtures were separated on 5% non-denaturing polyacrylamide gel in 0.5 × TBE buffer, transferred onto a nylon membrane and detected with a chemiluminescent system (Roche).

Allele-specific transcript quantification

ASTQ was carried out as described previously (27). Sequences of primers for PCR were shown in Supplementary Material, Table S5. Total RNA was extracted from PBMCs after stimulation for 4 h with 1 μg/ml of ionomycin and 50 ng/ml of PMA. Genomic DNAs and cDNAs were amplified for 36 cycles with the primers. At the last cycle, reverse primer labeled with Alexa Fluor 488 at the 5′ was added. Amplicons were digested with *Ban*II (Takara) according to manufacturer's instruction. Separation was conducted on 12% non-denaturing polyacrylamide gels in 25 mM Tris and 250 mM glycine. Visualization and quantification of digested and undigested PCR products was carried out by using FLA-7000 analyzer and Multiguage software (Fujifilm).

Accession codes

Genbank: human chromosome 4 genomic DNA sequence, NT_022792.17; mRNA sequences for human *CASP3*, NM_004346.3 and NM_032991.2.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at *HMG* online.

ACKNOWLEDGEMENTS

We thank the KD patients and their families as well as all the medical staff taking care of the patients. We are grateful to Tomoyo Matsubara, Makoto Nishibatake, Hiroyuki Aotsuka, Hiromichi Nakajima, Fumiyo Kudo, Ryota Ebata, Tetsuya Sano, Toru Matsushita, Kyoko Suzuki, Kunihiro Akagi, Takeshi Isobe, Satoko Ogita, Shozo Oku, Takeo Tanaka, Yuji Tanaka, Yuichi Nomura, Masako Sakauchi, Hideo Cho, Akiyoshi Nariai, Masaru Miura, Masao Nakagawa, Youichi Kaburagi and other pediatricians who contributed Japanese DNA samples. We appreciate Tomohiko Gunji for fruitful discussion. We thank Joan Pancheri, MSN and Nancy Innocentini RN for collection of DNA samples and DeeAnna Scherrer, Hiroko Sugiyama, Masako Saito, Saori Kawakami and Yoshie Kikuchi for technical assistance.

Conflict of Interest statement. None declared.

FUNDING

This work was supported by grants from the Millennium Project, from Japan Kawasaki disease Research Center and from the Ministry of Health, Labour and Welfare (0401040 to A.H.) and by a grant from the Heart, Lung and Blood Institute of the National Institutes of Health (HL-06941 to J.C.B.).

REFERENCES

1. Kawasaki, T. (1967) Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Arerugi*, **16**, 178–222.
2. Burns, J.C. (2002) Commentary: translation of Dr. Tomisaku Kawasaki's original report of fifty patients in 1967. *Pediatr. Infect. Dis. J.*, **21**, 993–995.
3. Kato, H., Koike, S., Yamamoto, M., Ito, Y. and Yano, E. (1975) Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. *J. Pediatr.*, **86**, 892–898.
4. Onouchi, Y., Tamari, M., Takahashi, A., Tsunoda, T., Yashiro, M., Nakamura, Y., Yanagawa, H., Wakui, K., Fukushima, Y., Kawasaki, T.

et al. (2007) A genomewide linkage analysis of Kawasaki disease: evidence for linkage to chromosome 12. *J. Hum. Genet.*, **52**, 179–190.
5. Onouchi, Y., Gunji, T., Burns, J.C., Shimizu, C., Newburger, J.W., Yashiro, M., Nakamura, Y., Yanagawa, H., Wakui, K., Fukushima, Y. *et al.* (2008) ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. *Nat. Genet.*, **40**, 35–42.
6. Yi, Q.J., Li, C.R. and Yang, X.Q. (2001) Effect of intravenous immunoglobulin on inhibiting peripheral blood lymphocyte apoptosis in acute Kawasaki disease. *Acta Paediatr.*, **90**, 623–627.
7. Tsujimoto, H., Takeshita, S., Nakatani, K., Kawamura, Y., Tokutomi, T. and Sekine, I. (2001) Delayed apoptosis of circulating neutrophils in Kawasaki disease. *Clin. Exp. Immunol.*, **126**, 355–364.
8. Woo, M., Hakem, R., Soengas, M.S., Duncan, G.S., Shahinian, A., Kägi, D., Hakem, A., McCurrach, M., Khoo, W., Kaufman, S.A. *et al.* (1998) Essential contribution of caspase 3/CPP32 to apoptosis and its associated nuclear changes. *Genes Dev.*, **12**, 806–819.
9. Hirota, J., Furuichi, T. and Mikoshiba, K. (1999) Inositol 1,4,5-trisphosphate receptor type 1 is a substrate for caspase-3 and is cleaved during apoptosis in a caspase-3-dependent manner. *J. Biol. Chem.*, **274**, 34433–34437.
10. Macián, F., García-Cózar, F., Im, S.H., Horton, H.F., Byrne, M.C. and Rao, A. (2002) Transcriptional mechanisms underlying lymphocyte tolerance. *Cell*, **109**, 719–731.
11. Northrop, J.P., Ho, S.N., Chen, L., Thomas, D.J., Timmerman, L.A., Nolan, G.P., Admon, A. and Crabtree, G.R. (1994) NF-AT components define a family of transcription factors targeted in T-cell activation. *Nature*, **369**, 497–502.
12. Sabbagh, L., Bourbonnière, M., Sékaly, R.P. and Cohen, L.Y. (2005) Selective up-regulation of caspase-3 gene expression following TCR engagement. *Mol. Immunol.*, **42**, 1345–1354.
13. Fischer, U., Jänicke, R.U. and Schulze-Osthoff, K. (2003) Many cuts to ruin: a comprehensive update of caspase substrates. *Cell Death Differ.*, **10**, 76–100.
14. Woo, M., Hakem, R., Furlonger, C., Hakem, A., Duncan, G.S., Sasaki, T., Bouchard, D., Lu, L., Wu, G.E., Paige, C.J. *et al.* (2003) Caspase-3 regulates cell cycle in B cells: a consequence of substrate specificity. *Nat. Immunol.*, **4**, 1016–1022.
15. Alam, A., Cohen, L.Y., Aouad, S. and Sékaly, R.P. (1999) Early activation of caspases during T lymphocyte stimulation results in selective substrate cleavage in nonapoptotic cells. *J. Exp. Med.*, **190**, 1879–1890.
16. Kennedy, N.J., Kataoka, T., Tschopp, J. and Budd, R.C. (1999) Caspase activation is required for T cell proliferation. *J. Exp. Med.*, **190**, 1891–1896.
17. Miossec, C., Dutilleul, V., Fassy, F. and Diu-Hercend, A. (1997) Evidence for CPP32 activation in the absence of apoptosis during T lymphocyte stimulation. *J. Biol. Chem.*, **272**, 13459–13462.
18. Puga, I., Rao, A. and Macián, F. (2008) Targeted cleavage of signaling proteins by caspase 3 inhibits T cell receptor signaling in anergic T cells. *Immunity*, **29**, 193–204.
19. Masuda, K., Takei, S., Nomura, Y., Imanaka, H., Sameshima, K. and Yoshinaga, M. (1998) Transient low T cell response to streptococcal pyrogenic exotoxin-C in patients with Kawasaki disease. *Pediatr. Res.*, **44**, 27–31.
20. Kollmann, T.R., Klein, E.J., Stefanelli, C.B. and Marcuse, E.K. (2001) Purified protein derivative anergy in Kawasaki disease. *Pediatr. Infect. Dis. J.*, **20**, 81–82.
21. Kuijpers, T.W., Wiegman, A., van Lier, R.A., Roos, M.T., Wertheim-van Dillen, P.M., Pinedo, S. and Ottenkamp, J. (1999) Kawasaki disease: a maturational defect in immune responsiveness. *J. Infect. Dis.*, **180**, 1869–1877.
22. Wu, W., Misra, R.S., Russell, J.Q., Flavell, R.A., Rincón, M. and Budd, R.C. (2006) Proteolytic regulation of nuclear factor of activated T (NFAT) c2 cells and NFAT activity by caspase-3. *J. Biol. Chem.*, **281**, 10682–10690.
23. Ayusawa, M., Sonobe, T., Uemura, S., Ogawa, S., Nakamura, Y., Kiyosawa, N., Ishii, M. and Harada, K. (2005) Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr. Int.*, **47**, 232–234.
24. Suzuki, A., Yamada, R., Chang, X., Tokuhiro, S., Sawada, T., Suzuki, M., Nagasaki, M., Nakayama-Hamada, M., Kawaida, R., Ono, M. *et al.* (2003) Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. *Nat. Genet.*, **34**, 395–402.
25. Spielman, R.S., McGinnis, R.E. and Ewens, W.J. (1993) Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am. J. Hum. Genet.*, **52**, 506–516.
26. Tregouet, D.A. and Garelle, V. (2007) A new JAVA interface implementation of THESIAS: testing haplotype effects in association studies. *Bioinformatics*, **23**, 1038–1039.
27. Uejima, H., Lee, M.P., Cui, H. and Feinberg, A.P. (2000) Hot-stop PCR: a simple and general assay for linear quantitation of allele ratios. *Nat. Genet.*, **25**, 375–376.

J Epidemiol 2010;20(4):302-307
doi:10.2188/jea.JE20090180

Original Article

Epidemiologic Features of Kawasaki Disease in Japan: Results of the 2007–2008 Nationwide Survey

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Received October 8, 2009; accepted January 8, 2010; released online June 5, 2010

Reprinted from

JEA

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Received October 8, 2009; accepted January 8, 2010; released online June 5, 2010

ABSTRACT

Background: The most recent epidemiologic features of Kawasaki disease (KD) are unknown.

Methods: The 20th nationwide survey of KD was conducted in 2009, and included patients treated for the disease in 2007 and 2008. Hospitals specializing in pediatrics, and hospitals with pediatric departments and 100 or more beds, were asked to report all patients with KD during the 2 survey years.

Results: From a total of 1540 departments and hospitals, 23 337 patients (11 581 in 2007 and 11 756 in 2008) were reported: 13 523 boys and 9814 girls. The annual incidence rates were 215.3 and 218.6 per 100 000 children aged 0–4 years in 2007 and 2008, respectively. These were the highest annual KD incidence rates ever recorded in Japan. The monthly number of patients peaked during the winter months; smaller increases were noted in the summer months. The age-specific incidence rate showed a monomodal distribution with a peak at age 9–11 months. The prevalences of both cardiac lesions during the acute phase of the disease and cardiac sequelae were higher among infants and older age groups.

Conclusions: The incidence rate and number of patients with KD in Japan continue to increase.

Key words: mucocutaneous lymph node syndrome; incidence; cardiovascular diseases; immunoglobulin, intravenous; epidemiology

INTRODUCTION

Kawasaki disease (KD) is a syndrome of unknown cause. It typically affects infants and toddlers, and causes systemic vasculitis.[1,2] Cardiac lesions, eg, coronary artery aneurysms, are a salient characteristic of the disease.[2–6] The most serious cardiac lesions are giant coronary aneurysms (those with a diameter ≥8 mm on 2-dimensional echocardiography), for which the prognosis is unfavorable. Prevention of these aneurysms is the primary target for pediatricians treating patients with KD.

Since 1970, nationwide epidemiologic surveys of KD have been conducted in Japan nearly every 2 years, and several features of the disease have been revealed.[7–11] The most recent previous survey, the 19th, included patients treated in 2005 and 2006, and revealed that both the annual number of patients and the incidence rate had increased linearly. If the trend were to continue, the annual incidence rate in 2008 would be higher than 200 per 100 000 population younger than 5 years.[10]

Herein, we report the results of the latest nationwide survey, for KD patients treated in 2007 and 2008.

METHODS

We conducted a retrospective survey of patients with KD visiting target hospitals for treatment of acute KD during the 2-year period from January 2007 through December 2008. The medical facilities that were requested to participate in the survey were hospitals specializing in pediatrics and hospitals with a pediatric department and 100 or more beds. These criteria have been used since the first nationwide survey in 1970.[12] Questionnaires and diagnostic guidelines prepared by the Japan Kawasaki Disease Research Committee[13] were sent by mail to administrators in charge of the pediatric department of their respective hospitals in January 2009. The prepared list of hospitals for the survey was based on the "Listing of Hospitals 2003–2004" compiled by the Committee on Studies of Health Policies, Ministry of Health, Labour and Welfare, Japan, and was revised using newly received information. A total of 2150 facilities met the conditions stated above.

The patient information requested on the questionnaire was: address (municipality), sex, date of birth, date and day of

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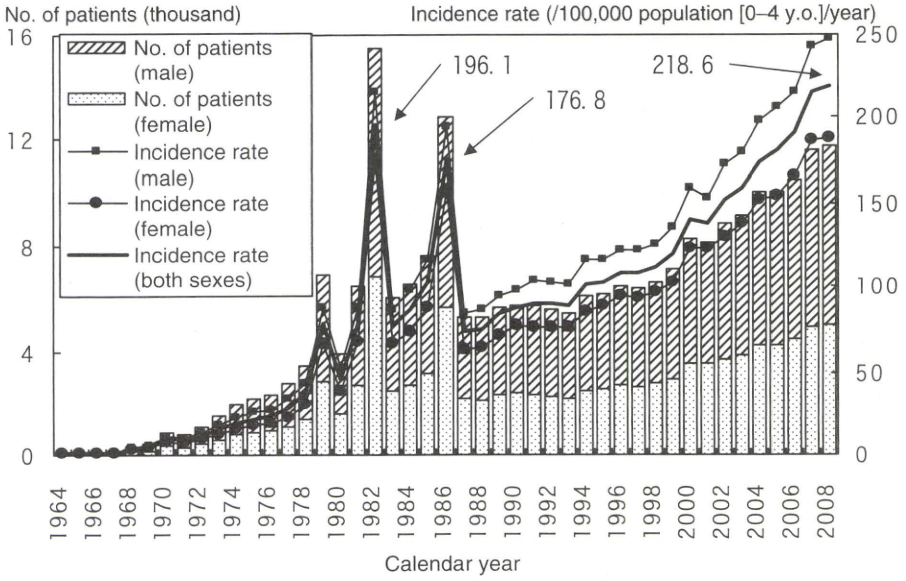

Figure 1. The number of patients with Kawasaki disease and incidence rate in Japan, by calendar year.

illness at first hospital visit, days of illness when discharged from the hospital, diagnosis (typical definite, atypical definite, and suspected), intravenous immunoglobulin (IVIG) therapy, additional therapy if conducted (additional IVIG therapy, steroids, infliximab, and immunosuppressive agents), recurrences, history of KD in patient's siblings and parents, cardiac lesions, and complications other than cardiac lesions such as arthralgia or arthritis, aseptic meningitis, hepatic abnormalities (serum aspartate aminotransferase ≥50 IU/L and/or alanine aminotransferase ≥50 IU/L), gallbladder swelling, paralytic ileus, facial nerve palsy, and disseminated intravascular coagulation (DIC). Acute cardiac lesions were defined as those that developed within 1 month of onset (acute lesions); cardiac sequelae were defined as those that persisted beyond 1 month after onset. Almost all patients were diagnosed on the basis of 2-dimensional echocardiography.

After checking for possible inconsistencies on the questionnaires, the forms were sent back to the respondents to correct any errors. The incidence rates were based on the population data used in the vital statistics of Japan.[14] The Ethical Board of Jichi Medical University approved this survey (November 11, 2008, No. 08-39).

RESULTS

Of the 2150 invitations sent requesting participation in the survey, 48 were returned because the pediatric department or the institution itself had closed. Of the remaining 2102 departments, 1540 (73.3%) responded to the survey and reported a total of 23 337 patients (11 581 in 2007 and 11 756 in 2008). There were 13 523 male patients and 9814 female patients. The average annual incidence rate for the observed 2-year period was 216.9 per 100 000 children aged 0–4 years (245.4 for boys and 187.0 for girls).

The annual numbers of patients with KD and the incidence rates in the 20 nationwide surveys, including this one, are shown in Figure 1. As previously reported, there were 3 large nationwide epidemics of the disease in Japan, in 1979, 1982, and 1986. Since then, there has been no nationwide epidemic, but the number of patients started to increase in the mid-1990s. Because of the decrease in the birth rate in Japan, the incidence rate increased more rapidly than did the number of patients, reaching 218.6 per 100 000 children aged 0–4 years in 2008. This was the first time that the incidence rate was higher than 200, and it surpassed the rates observed in 1979, 1982, and 1986, when the epidemics occurred.

Trends in the monthly number of patients observed in the previous 4 nationwide surveys (17th to 20th) are shown in Figure 2. The number was highest during the winter months in all years. There were also smaller increases during the summer months.

Age-specific incidence rates by sex are shown in Figure 3. As in previous surveys, the incidence rate was highest among children aged 6–11 months, after which it gradually decreased with advancing age.

Of the 23 337 patients reported, 18 620 (79.8%) were typical definite cases (patients with 5 or 6 of the symptoms specified in the diagnostic guidelines for KD), 648 (2.8%) were atypical definite cases (4 of the 6 symptoms plus coronary aneurysms including dilatation), and 4069 (17.4%) were suspected cases (those who did not satisfy the diagnostic criteria, but were suspected as having KD by the pediatricians reporting the cases). Of the 4069 suspected cases, 2661 (65.4%) had 4 of the 6 principal symptoms, 1063 (26.1%) had 3, 239 (5.9%) had 2, and 32 (0.8%) had 1.

The number of patients with a sibling affected by KD was 326 (1.4%); 165 (0.7%) patients had at least 1 parent with a history of KD. There were 823 (3.5%) recurrent cases. Of the 23 337 patients reported, 6 died.

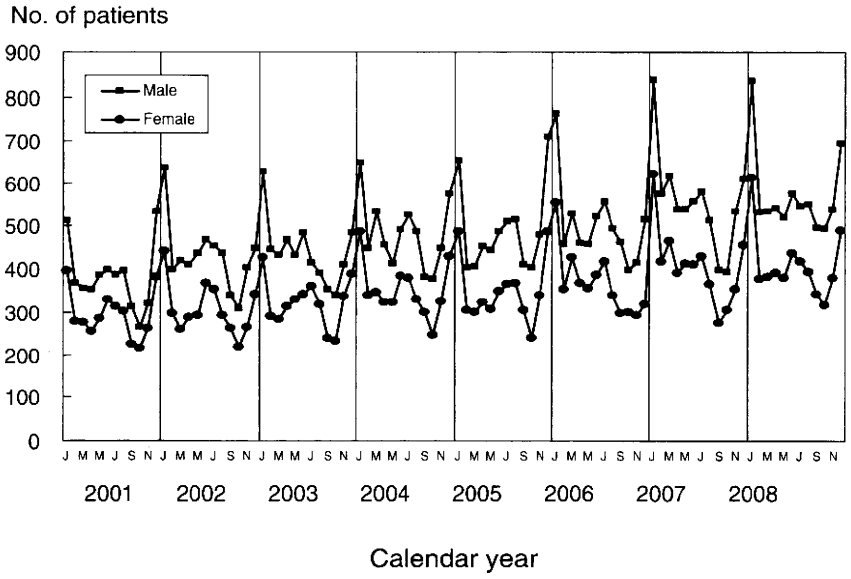

Figure 2. The number of patients with Kawasaki disease in Japan by month, 2001–2008.

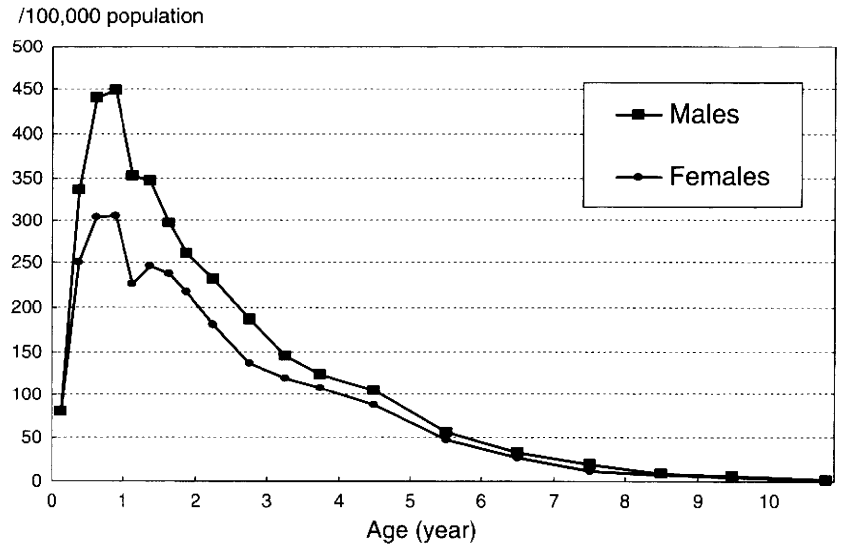

Figure 3. Age-specific annual incidence rate of Kawasaki disease in Japan, 2007–2008.

During the acute phase, 2577 (11.0%) patients had (a) cardiac lesion(s): 58 (0.25%) had giant coronary aneurysms, 282 (1.21%) had coronary aneurysms less than 8 mm in diameter, 1992 (8.54%) had coronary dilatations, 8 (0.03%) had coronary stenoses, 3 (0.01%) had myocardial infarctions, and 383 (1.64%) had valvular lesions. A total of 746 patients (3.2%) had cardiac sequelae 1 month after the onset of KD: 59 (0.25%) had giant coronary aneurysms, 188 (0.81%) had coronary aneurysms less than 8 mm in diameter, 435 (1.86%) had coronary dilatations, 5 (0.02%) had coronary stenoses, 2 (0.01%) had myocardial infarctions, and 114 (0.49%) had valvular lesions. As shown in Figure 4, cardiac abnormalities were more prevalent in boys than in girls, and in infants and older children (as compared with children aged 1–4 years).

Of the patients reported, 20313 (87.0%) received IVIG therapy. Of these, 3351 (16.5%) received additional IVIG therapy, 1173 (5.0%) were treated with steroids, 81 (0.35%) received infliximab, and 54 (0.23%) were treated with immunosuppressive agents.

Regarding patients with complications other than cardiac lesions, 1.13% had arthralgia or arthritis, 0.55% had aseptic meningitis, 27.4% had hepatic lesions, 1.62% had gallbladder swelling, 0.45% had paralytic ileus, 0.0% (1 patient) had facial nerve palsy, and 0.08% had DIC.

DISCUSSION

We presented the results of the 20th Nationwide Survey of Kawasaki Disease in Japan, which highlighted the most recent epidemiologic features of the disease. Since 1970, the

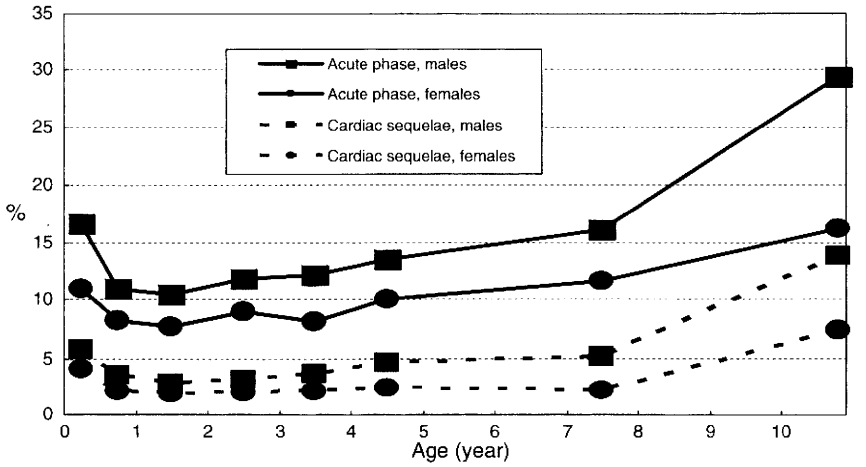

Figure 4. Age-specific prevalence of cardiac lesions and sequelae due to Kawasaki disease in Japan, 2007–2008.

nationwide surveys have been conducted almost every 2 years.[7–11] As shown in Figure 1, the number of patients and the incidence rate have dramatically increased since the mid-1990s. Even though there has been no nationwide epidemic of KD since 1986, the annual incidence rates in 2007 and 2008 were higher than those in the years of nationwide epidemics. Because the etiology of KD remains unknown, the reasons for these increases are also unclear. This increase is of concern and highlights the need for continued observation of the epidemiologic features of KD in Japan. Moreover, the results should motivate researchers to hasten their efforts to identify the cause of this disease.

The response rate of the survey was 73.3%, after 2 reminders were sent. Therefore, the actual number of patients was higher than that reported. However, data suggest that the real figures are at most 10% higher than the values we have reported.[15] We asked the departments and hospitals to respond to the survey even if they had not treated a KD patient during the 2-year period of the survey. However, despite this request, many of the nonresponding hospitals might have elected not to participate in the survey because they had treated no KD patients. Therefore, the underestimation is approximately 10%, despite a participation rate of only 70%.

There are factors that can potentially distort the reporting of chronological trends in KD. One of these factors is response rate, which was 73.3% in the current survey. The response rate was 70.7% for the 19th survey (2005–2006),[10] 70.1% for the 18th survey (2003–2004),[9] 68.0% for the 17th survey (2001–2002),[8] 66.5% for the 16th survey (1999–2000),[8] 68.5% for the 15th survey (1997–1998),[16] and 67.7% for the 14th survey (1995–1996).[16] As is evident, the response rates were similar. Thus, we do not believe that changes in the response rate affected the analysis of chronological change. Another issue would be a change in diagnostic criteria. In the current survey, the Fifth Revised Version of the Diagnostic Guidelines of Kawasaki Disease (2002) was used. Although the guidelines have been revised to account for the increased understanding of KD since the first nationwide survey in 1970, the principal points have not changed.[13] Therefore, the revision of the guidelines was unlikely to affect reporting of chronological changes. If the number of suspected cases increased, the clinical features of KD may also have changed. The proportion of suspected cases was 17.4% in the current survey, 14.3% in the 19th survey,[10] and 13.6% in the 18th survey.[9] Although there are no relevant data before the 18th survey, we do not believe that the proportion of suspected cases has increased to an extent that would affect the increases in the annual numbers of patients and incidence rates.

Even though the etiology of KD is unknown, the epidemiologic data suggest a relationship between the onset of the disease and infection.[17] One trend suggesting an infectious trigger is seasonal variation in the disease. As shown in Figure 2, the number of patients is always higher in winter. In addition, smaller peaks were observed in summer. Perhaps infectious agents—one prevalent in winter and the other in summer—triggered the onset of KD. Seasonal variations differ among countries and areas, even in the same hemisphere, whether north or south.[18] If the responsible infectious agents differ among countries and areas, this would explain variation in seasonal patterns among countries.

Regarding the age-specific incidence rate curve shown in Figure 3, a monomodal incidence rate curve was observed in the current survey, which indicates that there may be a relationship between disease occurrence and an infectious agent, in addition to the seasonal variation.[17] The low incidence rate just after birth might be due to the presence of passive immunity conferred from mothers, and the decrease after 1 year of age might be caused by herd immunity.

Cardiac lesions are of great concern in KD. Fortunately, the proportion of patients with cardiac sequelae has decreased year by year. The proportion was 7.0% in the 15th nationwide survey in 1997–1998,[19] 5.9% in the 16th (1999–2000),[8] 5.0% in the 17th (2001–2002),[8] 4.4% in the 18th (2003–2004),[9] and 3.8% in the 19th survey.[10] The proportion had been greater

than 10% in the early 1990s.[20] This improvement is due to progress in the diagnosis of KD, in identification of cardiac lesions, and in treatment, the core of which is IVIG therapy. Originally, the regimen for IVIG therapy was 200 mg or 400 mg per kilogram of body weight × 5 days, but this was changed to 2 g/kg for 1 day.[21,22] The reduction in cardiac sequelae is partly due to this change. However, KD is the main cause of acquired heart disease in childhood both in Japan[23] and in the United States,[24] and treatment to prevent cardiac lesions must continue to progress. The higher proportion of lesions among infants might be due to their immature circulation system, which is affected by vasculitis caused by KD[25]; the higher proportion observed among older children might be due to the difficulty in diagnosing KD at this age, as some older children display an atypical clinical course.[26] In this survey, 16.5% of patients treated with IVIG therapy received additional IVIG therapy, 5.0% were treated with steroids, and 0.4% and 0.2% were treated with infliximab and immunosuppressants, respectively. All of them may have been resistant to initial IVIG therapy during the acute phase. It is therefore important to identify the factors that predict such cases and the best treatment for such patients.

There are some limitations in the current survey. Because the etiology of the disease is unknown, there are no specific findings to aid in the diagnosis of the disease. Therefore, all the patients reported to the survey were diagnosed by pediatricians according to the diagnostic guidelines. Another problem is that some patients might have been reported by more than 1 hospital, as they may have been referred to another hospital due to the severity of the disease. In the 18th nationwide survey, 8.9% of the patients were referred from other hospitals, some of which were not included among the target hospitals for the survey, because of their small number of beds or the lack of pediatric departments; 4.9% of patients were referred to other facilities.[10] The proportion of double registrations is likely to be lower than these figures, and the effects on the overall results are unlikely to be substantial.

In conclusion, the number of patients and incidence rate of KD in Japan continue to increase year by year, and cardiac lesions remain an important concern. The monitoring of KD should therefore be continued.

ACKNOWLEDGEMENTS

The authors thank all the pediatricians who supported the nationwide surveys of Kawasaki disease in Japan. This study was partly financially supported by the Japanese Kawasaki Disease Research Center, which is a non-profit organization.

REFERENCES

1. Burgner D, Harnden A. Kawasaki disease: What is the epidemiology telling us about the etiology? Int J Infect Dis. 2005;9:185–94.
2. Falcini F. Kawasaki disease. Curr Opin Rheumatol. 2006;18:33–8.
3. Pahlavan PS, Niroomand F. Coronary artery aneurysm: a review. Clin Cardiol. 2006;29:439–43.
4. Imai Y, Sunagawa K, Ayusawa M, Miyashita M, Abe O, Suzuki J, et al. A fatal case of ruptured giant coronary artery aneurysm. Eur J Pediatr. 2006;165:130–3.
5. Freeman AF, Crawford SE, Cornwall ML, Garcia FL, Shulman ST, Rowley AH. Angiogenesis in fatal acute Kawasaki disease coronary artery and myocardium. Pediatr Cardiol. 2005;26:578–84.
6. Tsuda E, Hanatani A, Kurosaki K, Naito H, Echigo S. Two young adults who had acute coronary syndrome after regression of coronary aneurysms caused by kawasaki disease in infancy. Pediatr Cardiol. 2006;27:372–5.
7. Yanagawa H, Nakamura Y, Yashiro M, Kawasaki T, eds. Epidemiology of Kawasaki disease: a 30-year achievement. Tokyo: Shindan-to-Chiryosha; 2004.
8. Yanagawa H, Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K. Incidence of Kawasaki Disease in Japan: the Nationwide Surveys of 1999–2002. Pediatr Int. 2006;48:356–61.
9. Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K, Yanagawa H. Increasing incidence rate of Kawasaki disease in Japan: the nationwide survey. Pediatr Int. 2008;50:287–90.
10. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005–2006. J Epidemiol. 2008;18:167–72.
11. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Monthly observation of the numbers of patients and incidence rates of Kawasaki disease in Japan: chronological and geographical observation from nationwide surveys. J Epidemiol. 2008;18:273–9.
12. Yanagawa H. Summary of epidemiologic studies on Kawasaki disease in Japan. In: Yanagawa H, Nakamura Y, Yashiro M, Kawasaki T, eds. Epidemiology of Kawasaki disease: a 30-year achievement. Tokyo: Shindan-to-Chiryosha; 2004. p. 33–44.
13. Yanagawa H, Sonobe T. Cahnges in the diagnostic guidelines for Kawasaki disease. In: Yanagawa H, Nakamura Y, Yashiro M, Kawasaki T, eds. Epidemiology of Kawasaki disease: a 30-year achievement. Tokyo: Shindan-to-Chiryosha; 2004. p. 24–32.
14. Statistics and Information Department, Minister's Secretariat, ministry of health, Labour and Welfare. Vital statistics of Japan 2007, volume 1. Tokyo: Health and Welafare Statistics Association; 2009. p. 481–3.
15. Watanabe T, Oki I, Ojima T, Nakamura Y, Yanagawa H. An analysis of the number of patients with Kawasaki disease in Tochigi: using the data of the nationwide epidemiologic incidence survey and the public aid in Tochigi prefecture. Nippon Shonika Gakkai Zasshi. 2002;106:1892–5 (in Japanese).
16. Yashiro M, Yanagawa H. Database construction for information on patients with Kawasaki disease. In: Yanagawa H, Nakamura Y, Yashiro M, Kawasaki T, eds. Epidemiology of Kawasaki disease: a 30-year achievement. Tokyo: Shindan-to-Chiryosha; 2004. p. 57–77.
17. Shigematsu I. Significance and future problems of epidemiologic studies on Kawasaki disease. In: Yanagawa H, Nakamura Y, Yashiro M, Kawasaki T, eds. Epidemiology of Kawasaki disease:

a 30-year achievement. Tokyo: Shindan-to-Chiryosha; 2004. p. 1–5.
18. Wu MH, Nakamura Y, Burns JC, Rowley AH, Takahashi K, Newburger JW, et al. State-of-the-art basic and clinical science of Kawasaki disease: the 9th International Kawasaki Disease Symposium 10–12 April 2008, Taipei, Taiwan. Pediatr Health. 2008;2:405–9.
19. 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:e33.
20. Yanagawa H, Nakamura Y, Yashiro M, Ojima T, Koyanagi H, Kawasaki T. Update of the epidemiology of Kawasaki disease in Japan: from the results of 1993–94 nationwide survey. J Epidemiol. 1996;6:148–57.
21. Academic Committee of the Japanese Society of pediatric Cardiology and Cardiac Surgery. Guidelines for treatment of Kawasaki disease in acute phase. Nippon Shoni Junkanki Gakkai Zasshi (Pediatr Cardiol Cardiac Surg). 2004;20:54–62 (in Japanese).
22. Freeman AF, Shulman ST. Kawasaki disease: summary of the American Heart Association Guidelines. Am Fam Physician. 2006;74:1141–8.
23. Sonobe T. A summary of the epidemiologic surveys on Kawasaki disease conducted over 30 years. Jpn Med Assoc J. 2005;48:30–3.
24. Shulman ST, Rowley AH. Advances in Kawasaki disease. Eur J Pediatr. 2004;163:285–91.
25. Rosenfeld EA, Corydon KE, Shulman ST. Kawasaki disease in infants less than one year of age. J Pediatr. 1995;126:524–9.
26. Muta H, Ishii M, Sakaue T, Egami K, Furui J, Sugahara Y, et al. Older age is a risk factor for the development of cardiovascular sequelae in Kawasaki disease. Pediatrics. 2004;114:751–4.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2010) **52**, 790–794 doi: 10.1111/j.1442-200X.2010.03161.x

Original Article

Case–control study of giant coronary aneurysms due to Kawasaki disease: The 19th nationwide survey

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Abstract ***Background***: The risk factors for recently reported cases of giant coronary aneurysms due to Kawasaki disease have not been elaborated.

Methods: Fifty-three patients with giant coronary aneurysms, diagnosed as Kawasaki disease in 2005 and 2006, were selected from the 19th nationwide survey of the disease in Japan. With all the other patients recorded at the same hospitals as a control group, OR and their 95%CI were calculated to delineate the risk factors.

Results: In multivariate analyses, patients aged younger than 1 year (OR compared with 1–2-year-olds = 6.57) and those older than 5 years (OR compared with 1–2-year-olds = 4.24), those who received additional intravenous immunoglobulin (IVIG) without the use of steroid (OR = 8.38) and those who received steroid administration with or without the additional use of IVIG (OR = 220.51 and 83.83, respectively), showed significantly higher OR for giant coronary aneurysms. As for IVIG therapy, the additional use of IVIG (OR = 14.84), total dosage of IVIG exceeding 2500 mg/kg (OR compared with 1500–2499 mg/kg = 12.26) and the duration of IVIG administration for more than 3 days (OR = 30.12), were found to significantly increase the risk of developing giant aneurysms in univariate analyses that were adjusted for sex and age.

Conclusions: The observation of 53 patients with giant coronary aneurysms due to Kawasaki disease among those included in the nationwide survey presented some risk factors, together with considerations about the associated aneurysms.

Key words case–control studies, coronary aneurysm, epidemiology, immunoglobulins, intravenous, mucocutaneous lymph node syndrome.

One of the most serious problems associated with Kawasaki disease is the formation of giant coronary aneurysms. The recently-reported proportion of patients with giant aneurysms is approximately 0.3–0.4% in Japan.[1,2] Although this proportion is small, the existence of giant coronary aneurysms seriously affects the prognosis of the disease.[3,4]

Fortunately, in Japan, the proportion of patients with cardiac sequelae has decreased over time.[1,2,5–7] This declining trend was due to improvements in the diagnosis of the disease, the morphological evaluation of cardiac lesions and pharmacological therapies including intravenous immunoglobulin (IVIG) administration. Although the cause and pathophysiology of Kawasaki disease remain unknown, treatment is the only area of the disease in which firm evidence has been established from randomized clinical trials.[8–10] A single-infusion of high-dose immunoglobulin (2 g/kg per day), together with aspirin, currently constitutes the standard therapy for the acute stage of Kawasaki disease; but problems, such as the 10–20% of patients who do not respond to this therapeutic modality, and the need for long-term follow up of patients with cardiac sequelae, still remain.

Previously, our group conducted a case–control study using data obtained from the 15th and 16th nationwide surveys (1996–2000): in multivariate analyses, the study revealed that male sex, age younger than 1 year and the condition that developed to the fatal stage constituted significantly higher risks of developing giant coronary aneurysms.[11] In the same study, sex- and age-adjusted univariate analyses revealed the following as risk factors for giant aneurysms: an early start of IVIG therapy (1–3 days from onset); additional administration of IVIG; total dosages of IVIG exceeding 2500 mg/kg; the duration of IVIG administration lasting more than 3 days; and a regimen of 400 mg/kg IVIG × 5 days compared with 2 g/kg × 1-day regimen. In those days, however, only treatment with 400 mg/kg IVIG × 5 days was covered by the public medical insurance systems in Japan; and a 2 g/kg IVIG × 1-day regimen had been adopted in only a limited number of hospitals. Therefore, treatments for the disease differed among hospitals and pediatricians even within the same hospital. When the 19th nationwide survey was conducted for the patients in 2005 and 2006, however, a new regimen (2 g/kg IVIG × 1 day) had already been accepted by the public medical insurance systems; and this has been the standard therapy for the

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Received 21 July 2009; revised 8 February 2010; accepted 4 March 2010.

acute phase of the disease. As a result, the differences in the initial IVIG therapy for the disease among institutions have become minimal. On the contrary, for additional IVIG therapy and steroid therapy, regimens differ among institutions and standard therapies have not yet been established.

To elucidate the risk factors for giant coronary aneurysms due to Kawasaki disease, the data from the 19th nationwide survey of Kawasaki disease in Japan were examined and a case–control study was conducted. We endeavored to discover how the change in IVIG regimens affected the risk factors for giant coronary aneurysms. In addition, how additional IVIG therapy and steroid therapy influenced the probability of developing giant aneurysms was investigated.

Methods

The 19th nationwide survey of Kawasaki disease, sponsored by the Ministry of Health, Labour and Welfare of the Japanese government, was conducted in 2007 by the Japan Kawasaki Disease Research Committee. All hospitals with 100 or more beds and a pediatric department, as well as all pediatric hospitals, were asked to provide individual data on patients with Kawasaki disease who had been treated during a 2-year period from 2005 to 2006.

In the present survey, giant coronary aneurysms are defined as those having a diameter of 8 mm or more detected by echocardiography or coronary angiography one month after the onset of the disease. All the patients with giant coronary aneurysms who visited the hospital before the 10th day after the onset of Kawasaki disease were treated as the cases in this case–control study. All the other patients without giant coronary aneurysms who visited the same hospitals before the 10th day after onset served as controls. Patients who visited hospitals on the 10th day of illness or later were excluded from the category of either case or control because they were not observed at the most critical period during the natural course of the disease at the hospital that reported the patients to the nationwide surveillance system. Those who lacked any individual data for use in statistical analyses of this study were also excluded.

The presence or absence of related factors between the two groups with and without giant coronary aneurysms was compared. In this comparison, conditional logistic regression models with SPSS (version 13.0J) were used, and OR and their 95%CI were obtained (univariate analyses). In addition, several factors were included in the model at the same time to adjust for potential confounding factors (multivariate analyses).

Results

Over the 2-year period of observation, there were 53 patients who had Kawasaki disease with giant coronary aneurysms, thus being cases for the present study. A total of 1760 controls were selected according to the control-selection protocol.

Table 1 shows the characteristics of the 53 cases and 1760 controls who visited the hospitals before the 10th day of their illness. No fatal cases were found in either group in the present survey.

Table 1 Characteristics of cases and controls (19th nationwide survey in Japan, 2005–06)

	Cases (%) (n = 53)	Controls (%) (n = 1760)
Sex		
Male	37 (70)	105 (60)
Female	16 (30)	709 (40)
Age (years)		
0	22 (42)	451 (26)
1–2	8 (15)	718 (41)
3–4	9 (17)	388 (22)
≥5	14 (26)	203 (12)
Duration of illness at time of presentation to hospital (days)		
1–3 days	33 (62)	724 (41)
4–6 days	14 (26)	926 (53)
7–9 days	6 (11)	110 (6)
Diagnosis[†]		
Definite (typical)	48 (91)	1540 (88)
Definite (atypical) + Probable	5 (9)	220 (13)
Recurrence		
−	51 (96)	1690 (96)
+	2 (4)	70 (4)
Sibling cases		
−	52 (98)	1736 (99)
+	1 (2)	24 (1)
Fetal cases		
−	53 (100)	1760 (100)
+	0	0
IVGG therapy		
−	1 (2)	238 (14)
+	52 (98)	1522 (86)
Starting day of illness		
Without IVGG therapy	1 (2)	239 (14)
1–3 days	8 (15)	108 (6)
4–6 days	34 (64)	1196 (68)
≥7 days	10 (19)	217 (12)
Additional administration		
−	17 (32)	1500 (85)
+	36 (68)	260 (15)
Total dose		
Without IVGG therapy	1 (2)	238 (14)
<1500 mg/kg bodyweight	2 (4)	191 (11)
1500–2499 mg/kg bodyweight	14 (26)	1087 (62)
≥2500 mg/kg bodyweight	36 (68)	244 (14)
Duration of administration		
Without IVGG therapy	1 (2)	238 (14)
1–2 days	50 (94)	1517 (86)
≥3 days	2 (4)	5 (0.3)
Steroid therapy		
−	22 (42)	1701 (97)
+	31 (58)	59 (3)
Additional IVGG, steroid therapy		
+ +	25 (47)	43 (2)
− +	6 (11)	16 (1)
+ −	11 (21)	217 (12)
− −	11 (21)	1484 (84)

[†]A typical definite case is a patient with five or six symptoms of the guidelines of Kawasaki disease. An atypical case is a patient with four symptoms having cardiac lesions. A probable case is a patient with four symptoms not having any cardiac lesions. IVGG, intravenous gammaglobulin.

Table 2 Relationship between observed factors and the formation of giant coronary aneurysms

	Univariate	Univariate adjusted for sex and age	Multivariate
Sex			
Male	1.55 (0.85–2.82)		1.70 (0.83–3.50)
Female	1.00 (reference)		1.00 (reference)
Age (years)			
0	4.77 (2.08–10.92)		6.57 (2.40–17.93)
1–2	1.00 (reference)		1.00 (reference)
3–4	1.84 (0.70–4.84)		2.10 (0.72–6.14)
≥5	6.09 (2.48–14.96)		4.24 (1.40–12.85)
Duration of illness			
1–3 days	1.00 (reference)	1.00 (reference)	1.00 (reference)
4–6 days	0.34 (0.17–0.65)	0.40 (0.20–0.79)	1.18 (0.52–2.64)
7–9 days	0.99 (0.39–2.52)	1.12 (0.42–2.99)	3.09 (0.74–12.98)
Diagnosis			
Definite (typical)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Definite (atypical) + Probable	0.73 (0.28–1.90)	0.61 (0.23–1.66)	2.22 (0.68–7.29)
Recurrence			
−	1.00 (reference)	1.00 (reference)	1.00 (reference)
+	0.93 (0.22–3.98)	0.85 (0.20–3.72)	1.52 (0.30–7.63)
Sibling cases			
−	1.00 (reference)	1.00 (reference)	1.00 (reference)
+	1.14 (0.15–8.93)	1.33 (0.16–10.92)	0.88 (0.03–30.72)
Fetal cases			
−	1.00 (reference)	1.00 (reference)	1.00 (reference)
+	– –	– –	– –
IVGG therapy			
−	1.00 (reference)	1.00 (reference)	1.00 (reference)
+	7.98 (1.08–58.90)	7.65 (1.03–56.55)	2.97 (0.34–26.03)
Starting day of illness			
Without IVGG therapy	0.14 (0.02–1.02)	0.14 (0.02–1.08)	
1–3 days	2.73 (1.11–6.71)	2.51 (0.98–6.43)	
4–6 days	1.00 (reference)	1.00 (reference)	
≥7 days	1.36 (0.63–2.90)	1.31 (0.61–2.85)	
Additional administration			
−	1.00 (reference)	1.00 (reference)	
+	16.16 (8.20–31.84)	14.84 (7.56–29.12)	
Total dose			
Without IVGG therapy	0.27 (0.03–2.20)	0.32 (0.04–2.54)	
<1500 mg/kg bodyweight	0.26 (0.03–2.23)	0.28 (0.03–2.35)	
1500–2499 mg/kg bodyweight	1.00 (reference)	1.00 (reference)	
≥2500 mg/kg bodyweight	13.43 (6.72–26.82)	12.26 (6.10–24.64)	
Duration of administration			
Without IVGG therapy	0.04 (0.002–0.78)	0.03 (0.001–0.78)	
1–2 days	0.33 (0.04–2.87)	0.25 (0.02–2.91)	
≥3 days	1.00 (reference)	1.00 (reference)	
Steroid therapy			
−	1.00 (reference)	1.00 (reference)	
+	73.49 (31.25–172.85)	88.56 (34.39–228.07)	
Additional IVGG, steroid therapy			
+ +	153.78 (55.38–427.01)	188.81 (63.04–565.47)	220.51 (67.29–722.58)
− +	127.04 (24.92–647.75)	97.52 (17.25–551.28)	83.83 (13.47–521.58)
+ −	8.73 (3.45–22.13)	7.73 (3.05–19.60)	8.38 (3.13–22.47)
− −	1.00 (reference)	1.00 (reference)	1.00 (reference)

Data show the OR with 95%CI given in parentheses. IVGG, intravenous gammaglobulin.

Table 2 shows the OR and their 95%CI. In multivariate analyses, those aged younger than 1 year or older than 5 years compared with 1–2-year-olds, those who received additional IVIG administration without the use of steroid, and those who received steroid administration with or without the additional use of IVIG, were found to be associated with significantly higher risks of developing giant coronary aneurysms. For IVIG therapy, additional administration, total dosage exceeding 2500 mg/kg compared with 1500–2499 mg/kg and the duration of IVIG therapy for more than 3 days were observed as risk factors with statistical significance in univariate analyses that were adjusted for sex and age.

Discussion

Using the data from the 19th nationwide survey, the recent epidemiological features of giant coronary aneurysms due to Kawasaki disease during a 2-year period from 2005 to 2006 in Japan are presented. One of the most important problems associated with Kawasaki disease is the cardiac sequelae; thus the goal of treating the disease is to prevent these sequelae. Among these sequelae, the formation of giant coronary aneurysms is one of the most significant issues affecting the prognosis of the disease.[3,4]

Previously, our group conducted a case–control study of giant coronary aneurysms due to Kawasaki disease during a 4-year period from 1997 to 2000 in Japan by examining data taken from the 15th and 16th nationwide surveys.[11] The findings were very similar to those of the current study. In the earlier survey, laboratory data, such as hematocrit, leukocyte count, neutrophil count, hemoglobin, alanine aminotransferase (ALT) and sodium contents, were recorded.[11] Some of these parameters observed in the laboratory are component factors of Harada's score, which is the basis for the clinical application of IVIG.[12,13] However, no laboratory data were collected in the current survey, and for that reason, such laboratory data as described above could not be compared in this study.

In the present study, age younger than one year was observed as a significant risk factor for giant coronary aneurysms, and male sex showed a higher OR without statistical significance, which was probably due to the small sample size of this study. These findings were also shown in the earlier study to be of statistical significance.[11] Both factors have also been shown to constitute high risks for developing the disease in other countries[14–16] and are therefore included in Harada's score. This may mean that both factors affect the probability of developing coronary aneurysms. In this study, those patients who are older than 5 years were also found to be at a significantly higher risk of having giant aneurysms (a finding that coincided with the results of our previous study, although lacking statistical significance[11]). This may be explained by the difficulty in diagnosis and subsequent delay in treatments because some of these older patients showed an atypical clinical course of the disease.[17] The same tendency was also seen in this survey (data not shown).

Nowadays, a single infusion of high-dose (2 g/kg) immunoglobulin is the standard therapy for the acute stage of Kawasaki disease. Also, among all the patients observed in this survey, the initial administration regimens of IVIG consisted of 2 g/kg × 1 day (67.4%), 1 g/kg × 2 days (18.2%), 1 g/kg × 1 day (10.1%), 2 g/kg × 2 days (0.2%) and other medication schedules (4.1%). When our previous survey was conducted, the public medical insurance systems in Japan covered only the treatment with 400 mg/kg IVIG × 5 days; therefore, a high-dose infusion regimen of IVIG was only adopted in a limited number of hospitals. Although this difference in the IVIG regimen might influence results, similar findings were also observed in this study. Administration of additional IVIG, total dosage of IVIG exceeding 2500 mg/kg and the duration of IVIG therapy for more than 3 days showed significantly higher OR for giant coronary aneurysms in the present study. These results are reasonable because pediatricians may diagnose severe cases at an early stage and decide to administer IVIG beyond its conventional dosage.

Currently, 10–20% of patients who do not respond to the initial treatment with IVIG are frequently treated with an additional dosage of IVIG and/or steroids, as recommended in the guidelines presented by the American Heart Association.[18] With regard to steroid therapy, however, there has been a longstanding controversy about its efficacy in preventing coronary aneurysms. Recently, a multicenter randomized controlled trial showed no superiority in adding methylprednisolone pulse therapy to the conventional IVIG therapy.[19] On the other hand, some studies showed the efficacy of steroid therapy in the acute stage of Kawasaki disease.[20,21] In the current study, steroid administration with or without the additional use of IVIG showed a significantly higher OR for giant aneurysms. The result seems reasonable if one considers that pediatricians may decide to administer steroid compounds to patients considering their degree of resistance to the initial or subsequent additional IVIG therapy.

Unfortunately, because the present study is not an interventional but rather an observational study, we cannot draw definitive conclusions. This is the greatest limitation to the discussion in this study. A multicenter randomized controlled trial is required to obtain conclusive results. If we had matched all cases to the control patients in the baseline laboratory data included in Harada's score, which were not collected in this survey, we could have revealed which therapy was most effective to prevent giant coronary aneurysms. This is also an important limitation.

In conclusion, 53 cases with giant coronary aneurysms due to Kawasaki disease were reported in the 19th nationwide surveys. The examination of these cases provided some risk factors, such as age younger than 1 year and older than 5 years, additional IVIG therapy and steroid therapy, together with considerations about the associated aneurysms.

Acknowledgments

This research was conducted as a research project of The Japan Kawasaki Disease Research Committee sponsored by the Ministry of Health, Labour and Welfare of the Japanese government. The authors thank all the pediatricians supporting the nationwide survey of Kawasaki disease in Japan, and express special thanks to Ms Hiroko Sudo (School of Nursing Affiliated with Dokkyo Medical University), who is a data-processing specialist.

References

1 Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K, Yanagawa H. Increasing incidence of Kawasaki disease in Japan: Nationwide survey. *Pediatr. Int.* 2008; **50**: 287–90.
2 Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: Results from the nationwide survey in 2005–06. *J. Epidemiol.* 2008; **18**: 167–72.
3 Kato H, Sugimura T, Akagi T *et al.* Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation* 1996; **94**: 1379–85.

4 Suzuki N, Seguchi M, Kouno C, Inukai K, Kito H, Kobayashi H. Rupture of coronary aneurysm in Kawasaki disease. *Pediatr. Int.* 1999; **41**: 318–20.
5 Yanagawa H, Nakamura Y, Yashiro M, Ojima T, Koyanagi H, Kawasaki T. Update of the epidemiology of Kawasaki disease in Japan – from the results of 1993–94 nationwide survey. *J. Epidemiol.* 1996; **6**: 148–57.
6 Yanagawa H, Nakamura Y, Yashiro M *et al.* Incidence survey of Kawasaki disease in 1997 and 1998 in Japan. *Pediatrics* 2001; **107**: 1–4.
7 Yanagawa H, Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K. Incidence of Kawasaki disease in Japan: The nationwide surveys of 1999–2002. *Pediatr. Int.* 2006; **48**: 356–61.
8 Furusho K, Kamiya T, Nakano H *et al.* High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984; **2**: 1055–8.
9 Newburger JW, Takahashi M, Burns JC *et al.* The treatment of Kawasaki syndrome with intravenous gamma globulin. *N. Engl. J. Med.* 1986; **315**: 341–7.
10 Newburger JW, Takahashi M, Beiser AS *et al.* A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N. Engl. J. Med.* 1991; **324**: 1633–9.
11 Nakamura Y, Yashiro M, Uehara R *et al.* Case–control study of giant coronary aneurysms due to Kawasaki disease. *Pediatr. Int.* 2003; **45**: 410–3.
12 Harada K. Intravenous gamma-globulin treatment in Kawasaki disease. *Acta Paediatr. Jpn.* 1991; **33**: 805–10.
13 Sato N, Sugimura T, Akagi T *et al.* Selective high dose γ-globulin treatment in Kawasaki disease: Assessment of clinical aspects and cost effectiveness. *Pediatr. Int.* 1999; **41**: 1–7.
14 Harnden A, Alves B, Sheikh A. Rising incidence of Kawasaki disease in England: Analysis of hospital admission data. *BMJ* 2002; **324**: 1424–5.
15 Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics* 2003; **112**: 495–501.
16 Park YW, Han JW, Park IS *et al.* Kawasaki disease in Korea, 2003–05. *Pediatr. Infect. Dis. J.* 2007; **26**: 821–3.
17 Muta H, Ishii M, Sakaue T *et al.* Older age is a risk factor for the development of cardiovascular sequelae in Kawasaki disease. *Pediatrics* 2004; **114**: 751–4.
18 Kavey RE, Allada V, Daniels SR *et al.* Cardiovascular risk reduction in high-risk pediatric patients: A scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics. *Circulation* 2006; **114**: 2710–38.
19 Newburger JW, Sleeper LA, McCrindle BW *et al.* Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N. Engl. J. Med.* 2007; **356**: 663–75.
20 Jibiki T, Terai M, Kurosaki T *et al.* Efficacy of intravenous immune globulin therapy combined with dexamethasone for the initial treatment of acute Kawasaki disease. *Eur. J. Pediatr.* 2004; **163**: 229–33.
21 Inoue Y, Okada Y, Shinohara M *et al.* A multicenter prospective randomized trial of corticosteroids in primary therapy for Kawasaki disease: Clinical course and coronary artery outcome. *J. Pediatr.* 2006; **149**: 336–41.

J Epidemiol 2010;20(6):429-432
doi:10.2188/jea.JE20100006

Original Article

Characteristics and Validity of a Web-Based Kawasaki Disease Surveillance System in Japan

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Received January 14, 2010; accepted June 7, 2010; released online August 28, 2010

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Received January 14, 2010; accepted June 7, 2010; released online August 28, 2010

ABSTRACT

Background: Although regular nationwide surveys of Kawasaki disease (KD) are conducted in Japan, there is no system for detecting the real-time epidemic status of this disease.

Methods: A web-based surveillance system for KD was developed. After consideration of the number of patients reported by prefecture to the 19th nationwide survey, 355 pediatric departments were asked to participate in the surveillance, and 225 agreed. Since January 2008, pediatricians in these 225 hospitals have reported KD patient data immediately after diagnosis. The daily numbers of patients are available to the public via the internet at http://www.kawasaki-disease.net/kawasakidata/. The validity of the data in 2008 was evaluated using the Japanese 20th nationwide survey of KD as the gold standard.

Results: A total of 3376 patients were reported to the web-based surveillance system from the 1st week through 52nd week of 2008. The number of patients reported to the nationwide survey during the same period was 11 680: a total of 4950 patients from the hospitals participating in the web-based surveillance and 6730 from other hospitals. The epidemic curves were similar, and the correlation coefficient between the web-based surveillance and the total numbers in the nationwide survey was 0.806 ($P < 0.01$).

Conclusions: The web-based surveillance system for Kawasaki disease in Japan demonstrated good validity.

Key words: mucocutaneous lymph node syndrome; incidence; epidemiology; sentinel surveillance; internet

INTRODUCTION

Kawasaki disease (KD) affects mainly infants and toddlers. The number of patients with KD and its incidence rate have increased year by year in Japan, and the total number of patients who have received a diagnosis of KD in Japan is 249 019.[1] However, the etiology of the disease remains unknown. Nationwide epidemiologic surveys are conducted every 2 years to observe the epidemiologic features of the disease in Japan.[1,2] Many epidemiologic and clinical features have been revealed by analyzing the data from these surveys, but the surveys have some limitations. One of the most important of these is time lag. Because the survey is biennial, we do not obtain information on the real-time frequency of KD.

To solve this problem, a research committee established a KD surveillance system and asked pediatricians to use a postcard to continuously report the monthly number of patients.[3–5] This committee-based monthly surveillance ended in 1996, after KD was designated as a target infectious disease. As a result of this new designation, KD became part of a weekly national surveillance system for infectious diseases conducted by the Japanese Ministry of Health and Welfare (currently the Ministry of Health, Labour and Welfare). The validity of this national surveillance system was confirmed in a comparison with data from the nationwide surveys.[6] However, this national surveillance system was changed in 1999, after the Infectious Disease Prevention Act of 1900 was superceded by the current Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases Act of 1998, which excluded KD from the list of target diseases subject to national surveillance.[6] As a result, there was no real-time surveillance of KD in Japan from 1999 until 2007.

In 2007, the Research Committee on Study on the Construction of Comprehensive Data Base about the Chronic Diseases of Children (Chairman: Dr. Shohei Harada)

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established a new web-based surveillance system for KD in Japan. The system started in October 2007, and a fully operational system has been available since January 2008. In this report, we explain the web-based surveillance system and evaluate its validity using data from the 20th nationwide survey of KD.

METHODS

The web-based surveillance system for KD was constructed by a communication company (Ohmi Computer System, Ltd.). Immediately after a diagnosis of KD is made by a pediatrician, patient data are entered, including patient name (initials only), sex, address (municipality name only), date of birth, date of onset, date of first visit to the medical institution, date of diagnosis, and diagnosis (typical definite: 5 or 6 of the principal symptoms, according to the diagnostic guidelines of the disease[7]; atypical definite: 4 principal symptoms plus cardiac lesion[s]; suspected type A: 4 principal symptoms without cardiac lesions; and suspected type B: 3 or fewer principal symptoms and cardiac lesion[s]). The registered data are entered on a personal computer by the pediatrician, encrypted, sent to a server of the communication company, and stored using a secure system requiring passwords. The daily numbers of patients registered can be seen in real-time by the public via the internet (http://www.kawasaki-disease.net/kawasakidata/). Information on the age and sex distribution of all registered patients is also available. In addition, a pediatrician can analyze patient data that he/she has registered, and participating hospitals can observe the epidemic curve by district.

In 2007, we recruited hospitals from which pediatricians would enter patient data into the system. Using data from the 19th nationwide survey of KD,[2] we identified the hospitals that reported the 3 highest numbers of patients in each prefecture and asked them to participate in the web-based surveillance; any additional hospitals with 26 or more patients during the period from 2005 through 2006 (the target years of the 19th survey) were also asked to participate. Ultimately, 355 hospitals were asked to participate in the web-based surveillance system, and 225 eventually did so. Pediatricians in these 225 hospitals have entered the required patient data since October 2007.

The validity of the web-based surveillance system was evaluated using the 20th nationwide survey of KD[1] as the gold standard. The weekly numbers of patients (from Monday through Sunday) who first visited a hospital because of KD in 2008 were calculated using data from the web-based surveillance system and the 20th nationwide survey. In detail, the weekly numbers of patients for the 2 surveys were compared from the 1st week of 2008, which started on 31 December 2007, through the 52nd week, which ended on 28 December 2008. In addition to the overall analysis, data from the nationwide survey were classified by whether the hospital had participated in the web-based surveillance system or not. The correlation coefficients (degrees of freedom = 50) between the weekly numbers of patients reported to the web-based surveillance and nationwide survey were calculated.

The Ethical Committee on Epidemiologic Research of Jichi Medical University approved the study (13 September 2007, Eki 07-17).

RESULTS

The web-based surveillance system has been fully operational since January 2008, and 5837 patients were reported by the end of 2009 (http://www.kawasaki-disease.net/kawasakidata/). In January 2009, 10 to 20 new patients were reported to the system each day. The daily number of new patients subsequently declined to 5 to 10, as shown in Figure 1. Since July 2009, the daily number was approximately 5. The number of male patients was 3325, and the number of females was 2480 (the sex of 32 patients is unknown). The age distribution peaked at 6 to 11 months. These findings were similar to the epidemiologic features reported in the nationwide surveys.[1,2]

A total of 3376 patients were reported by the 225 hospitals participating in the web-based surveillance system from the 1st through the 52nd week of 2008. The number reported to the nationwide survey was 11 680 (4950 patients from the 225 hospitals participating in the web-based surveillance and 6730 from other hospitals). Figure 2 shows the weekly numbers of patients from the 2 data sources. The epidemic curves were similar, and the correlation coefficient was 0.806 for the total numbers of patients reported to the web-based system and the 20th nationwide survey, 0.852 for the web-based surveillance data and data from the 20th nationwide survey reported by hospitals participating in the web-based surveillance, and 0.694 for the web-based surveillance data and data from the 20th nationwide survey reported by other hospitals. All the coefficients were significant ($P < 0.01$).

DISCUSSION

In this report, we described the current state of a web-based surveillance system for KD and noted its high validity in comparison with data from the 20th nationwide survey of the disease. Because as many as 225 hospitals have participated in the web-based surveillance, the data collected are valid, and we are able to observe the real-time epidemic curve of KD in Japan.

Although there have been approximately 250 000 patients with KD in Japan, the etiology of the disease remains unknown. However, epidemiologic data indicate that an infectious agent or agents is related to the onset of KD, as there have been 3 nationwide epidemics, in 1979, 1982,

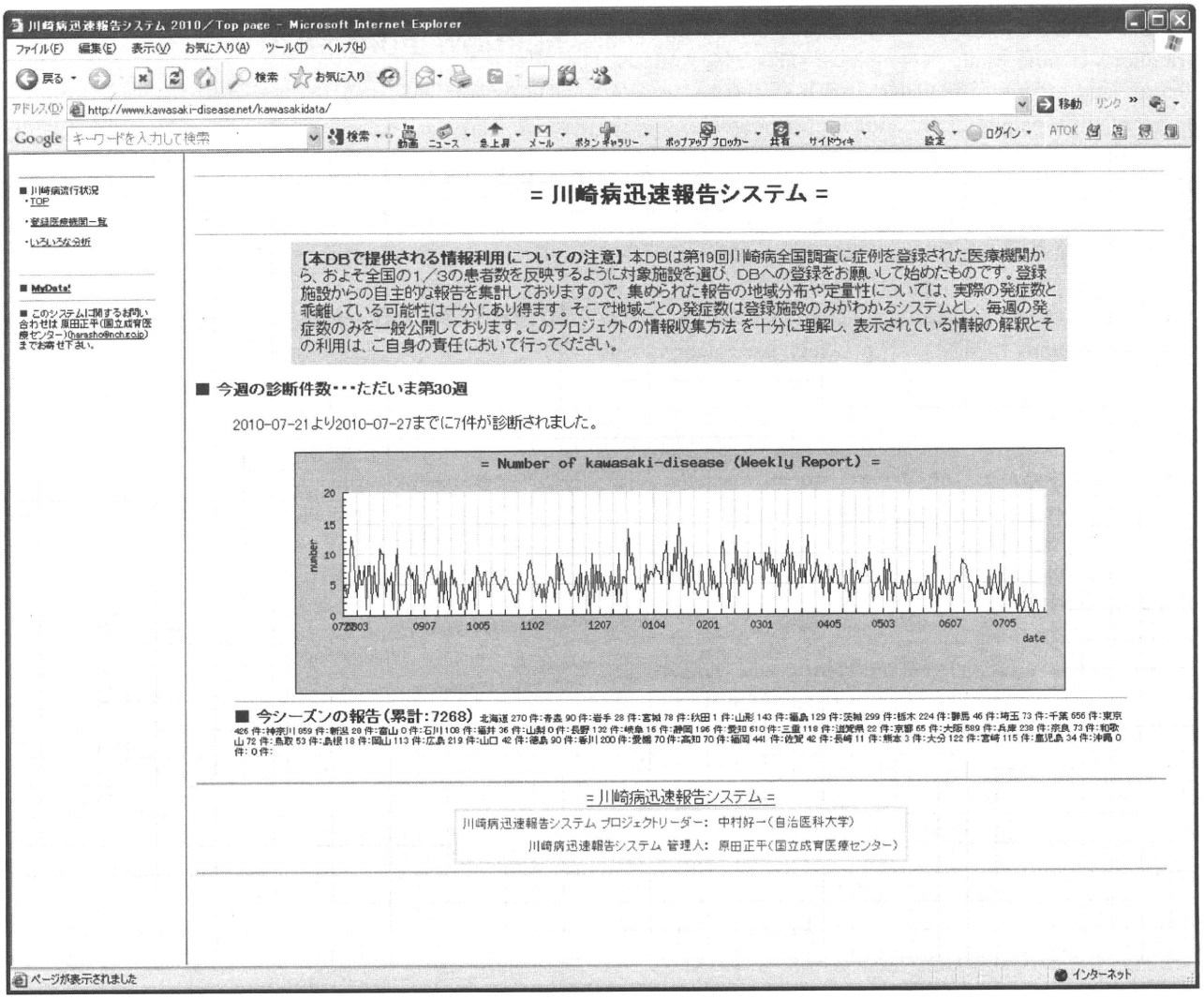

Figure 1. System used for surveillance of Kawasaki disease (screenshot)
http://www.kawasaki-disease.net/kawasakidata/

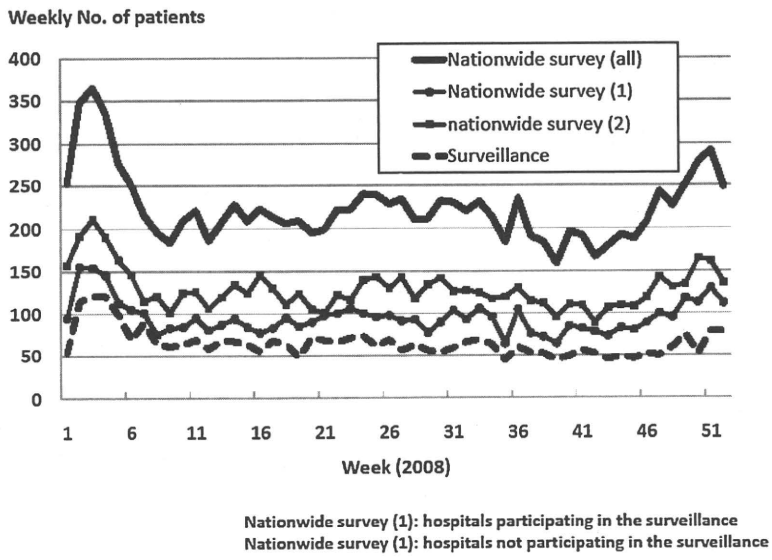

Figure 2. Weekly numbers of patients with Kawasaki disease reported to the internet surveillance system and the 20th nationwide survey in 2008.

and 1986,[1,2] and investigators have noted a monomodal age distribution,[1,2] time and geographical clustering of the patients,[8] and a high frequency of the disease among siblings of KD patients.[8] In addition, nationwide survey data[8] revealed seasonal incidence, which has also been noted in other countries.[9] Thus, we believe that it is important to monitor the number of patients with KD, as is done with infectious diseases, even though KD is not certified as infectious.

There have been several validation studies of KD surveillance systems in Japan, all of which used nationwide survey data as the gold standard.[6,10,11] In this study we also used these data as the gold standard.

Many hospitals joined the web-based surveillance system because of 2 advantages: they are able to use their the own data in the system and they can observe detailed analyses. The former means that a pediatrician can use his/her registering data via the internet, and the latter allows observation of epidemic curves by district. These 2 advantages are incentives for participation.

Of the 11 680 KD patients reported to the nationwide survey for 2008, 3376 were posted to the web-based surveillance system as well, a proportion of 28.9%. In the previous postcard surveillance system administered by the research committee, the reported number of patients was approximately one-third that reported to the nationwide survey for the corresponding time period.[3] Because the previous system was able to detect the third nationwide epidemic of the disease, in 1986,[3,5] we believe that the size of the current web-based surveillance system is sufficient for detecting epidemics, as its sample size is similar to that of the previous system.

The large number of participating hospitals ensured that the data of the web-based surveillance system had high validity, as determined using the nationwide survey as gold standard. Correlation coefficients are the main index of the external validity for continuous data,[12] and all were close to 1.0 in the present study. The epidemic curve of patients from hospitals not participating in the web-based surveillance was fairly similar to that of patients from participating hospitals. These results imply that the number of patients from non-participating hospitals increased when the total number of patients increased, because the numbers of patients with KD per hospital were somewhat smaller than those in participating hospitals. This indicates that patients with KD visited hospitals without consideration of the number of patients visiting the hospitals. Therefore, the epidemic curve based on the surveillance data resembled the gold standard, ie, the epidemic curve from the nationwide survey data.

In conclusion, the current web-based surveillance of KD demonstrated good validity.

ACKNOWLEDGMENTS

The authors thank all the pediatricians participating in the surveillance of Kawasaki disease. This study was partly financially supported by a Research Grant for "Research on Children and Families" by the Japanese Ministry of Health, Labour and Welfare.

REFERENCES

1. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Chihara I, Aoyama Y, et al. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2007–2008. J Epidemiol. 2010;20:302–7.
2. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005–2006. J Epidemiol. 2008;18:167–72.
3. Yanagawa H, Nakamura Y, Fujita Y, Nagai M, Aso S, Imada Y, et al. Estimation of the incidence of Kawasaki disease on basis of surveillance. Nippon Shonika Gakkai Zasshi. 1988;92:1754–9 (in Japanese with English abstract).
4. Yashiro M, Nakamura Y, Hirose K, Yanagawa H, Kato H, Okawa S, et al. Surveillance of Kawasaki disease in Japan: results of 9 years. Shonika. 1994;35:553–9 (in Japanese).
5. Yanagawa H, Yashiro M, Nakamura Y, Hirose K, Kawasaki T. Nationwide surveillance of Kawasaki disease in Japan, 1984 to 1993. Pediatr Infect Dis J. 1995;14:69–71.
6. Nakamura Y, Yashiro M, Yanagawa H. Validity of the infectious disease surveillance system on comparison of nationwide survey of Kawasaki disease during a 10 year period. Nippon Koshu Eisei Zasshi. 2000;47:1029–35.
7. Yanagawa H, Sonobe T. Cahnges in the diagnostic guidelines for Kawasaki disease. In: Yanagawa H, Nakamura Y, Yashiro M, Kawasaki T, eds. Epidemiology of Kawasaki disease: a 30-year achievement. Tokyo: Shindan-to-Chiryosha; 2004. p. 24–32.
8. Yanagawa H. Summary of epidemiologic studies on Kawasaki disease in Japan. In: Yanagawa H, Nakamura Y, Yashiro M, Kawasaki T, eds. Epidemiology of Kawasaki disease: a 30-year achievement. Tokyo: Shindan-to-Chiryosha; 2004. p. 33–44.
9. Wu MH, Nakamura Y, Burns JC, Rowley AH, Takahashi K, Newburger JW, et al. State-of-the-art basic and clinical science of Kawasaki disease: the 9th International Kawasaki Disease Symposium 10–12 April 2008, Taipei, Taiwan. Pediatr Health. 2008;2:405–9.
10. Nakamura Y. Estimation of epidemic by using surveillance data: about Kawasaki disease in Fukuoka Prefecture. Nippon Eiseigaku Zasshi. 1986;41:836–42 (in Japanese with English abstract).
11. Yashiro M, Sakata K, Nakamura Y, Yanagawa H. Evaluation of a nationwide surveillance system for Kawasaki disease over aneleven-year period from 1984. Nippon Koshu Eisei Zasshi. 1996;43:102–10 (in Japanese with English abstract).
12. Szklo M, Mieto FJ. Epidemiology: beyond the basics, 2nd ed. Sudbury: Jones and Bartlett; 2007. p. 333–43.