Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of the Formosan Medical Association (2014) 113, 148–154

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Viral infections associated with Kawasaki disease

Luan-Yin Chang [a,*], Chun-Yi Lu [a], Pei-Lan Shao [a], Ping-Ing Lee [a], Ming-Tai Lin [a], Tsui-Yien Fan [a], Ai-Ling Cheng [a], Wan-Ling Lee [a], Jen-Jan Hu [b], Shu-Jen Yeh [c], Chien-Chih Chang [d], Bor-Luen Chiang [a], Mei-Hwan Wu [a], Li-Min Huang [a,*]

[a] *Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan*
[b] *Department of Pediatrics, Taiwan Adventist Hospital, Taipei, Taiwan*
[c] *Department of Pediatrics, Far Eastern Memorial Hospital, New Taipei City, Taiwan*
[d] *Department of Pediatrics, Min-Sheng General Hospital, Tao-Yuan, Taiwan*

Received 22 October 2013; received in revised form 25 December 2013; accepted 28 December 2013

KEYWORDS
Kawasaki disease;
virus

Background/Purpose: Kawasaki disease (KD) is a disease of unknown cause. To investigate the infectious etiology of Kawasaki disease, we initiated a prospective case-control study to investigate possible links between common viral infections and Kawasaki disease.
Methods: We enrolled 226 children with KD and 226 age- and sex-matched healthy children from February 2004 to March 2010. Throat and nasopharyngeal swabs were taken for both viral isolation and polymerase chain reaction (PCR) for various viruses.
Results: The mean age of the 226 KD cases was 2.07 years, and the male to female ratio was 1.43 (133 boys to 93 girls). Their mean fever duration was 7.5 days with a mean peak temperature of 39.7°C. In addition to the typical symptoms of fever, neck lymphadenopathy, lip fissure and/or strawberry tongue, skin rash, nonpurulent bulbar conjunctivitis, palm/sole erythema, and induration followed by periungual desquamation, these KD cases also exhibited cough (69%), rhinorrhea (58%), and diarrhea (45%). Cases of KD had a significantly higher positive rate of viral isolation in comparison with the control group (7.5% vs. 2.2%, $p = 0.02$). Compared with the control group, cases of KD were more likely to have overall positive rates of viral PCR (50.4% vs. 16.4%, $p < 0.001$) and for various viruses including enterovirus (16.8% vs. 4.4%, $p < 0.001$), adenovirus (8.0% vs. 1.8%, $p = 0.007$), human rhinovirus (26.5% vs. 9.7%, $p < 0.001$), and coronavirus (7.1% vs. 0.9%, $p = 0.003$).

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding authors. Division of Pediatric Infectious Diseases, Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, Number 8, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail addresses: ly7077@tpts6.seed.net.tw, lychang@ntu.edu.tw (L.-Y. Chang), lmhuang@ntu.edu.tw (L.-M. Huang).

http://dx.doi.org/10.1016/j.jfma.2013.12.008

Conclusion: We found that some common respiratory viruses, such as adenoviruses, enteroviruses, rhinoviruses, and coronaviruses, were associated with KD cases.

Introduction

Kawasaki disease (KD) is an acute systemic febrile illness of unknown etiology which predominantly affects children under 5 years of age. Initially described in 1967 by Tomisaku Kawasaki,[1] it is now the most common cause of acquired heart diseases in children in the developed world due to the less frequent occurrence of rheumatic heart disease. There have been reports of differing incidence rates in different countries. Asian countries are supposed to have higher incidences of KD (30—200/per 100,000 children under 5 years of age) than most of the Western countries (3.5—10/per 100,000 children under 5 years of age).[2—10]

The etiology of KD is still controversial and infections are considered to be one of the predisposing factors. The infectious evidence of Kawasaki disease includes temporal clustering and marked seasonality, geographic clustering, family clustering, a high association between Kawasaki disease and infectious disease surveillance, and age distribution, for which the highest incidence rates are seen among 6 month—2-year-old children who have low maternal antibodies and are most susceptible to infections in general.[11—14] We hypothesize that infections with certain viruses may elicit systemic inflammation, and further small and median sized vasculitis, so-called Kawasaki disease, in certain hosts because we found a higher incidence of KD among males, young children, and Asian populations. We thus carried out a prospective case-control study to investigate the association of common viral infections with Kawasaki disease to test the above hypothesis.

Patients and methods

Case enrollment

From February 2004 to March 2010, we enrolled patients who fulfilled the Kawasaki disease criteria at the National Taiwan University Hospital in Taipei City, Taiwan and other collaborative hospitals including Taiwan Adventist Hospital in Taipei City, Far Eastern Memorial Hospital in New Taipei City, and Min-Sheng Hospital in Tao-Yuan County, Taiwan.

We enrolled Kawasaki disease cases that had fever for over 5 days and at least four of the following five manifestations: neck lymphadenopathy, lip fissure and/or strawberry tongue, skin rash, nonpurulent bulbar conjunctivitis, palm/sole erythema, and induration followed by periungual desquamation. The onset of KD illness cases was defined as the 1st day of fever onset.

After informed consent was obtained from the parents, a questionnaire-styled interview was carried out to solicit clinical symptoms and previous contact history with ill household members or with ill people from outside of the household. The illness included sore throat, rash, fever, conjunctivitis, cough, rhinorrhea, abdominal pain, and diarrhea. Clinical laboratory data and coronary arterial lesions were collected from the participants, and all received intravenous immunoglobulin 2 g per Kg plus low-dose aspirin (3—5 mg per Kg). If fever persisted for 2 days after use of intravenous immunoglobulin, retreatment with intravenous immunoglobulin was administered.

Two-dimensional echocardiography was performed in all patients during hospitalization and was repeated at convalescence, 2 weeks, and 8 weeks after discharge. Coronary arterial lesions were defined as coronary arterial dilatation/ectasia, aneurysm, and increased echogenecity, irregularity of vascular wall, or coronary artery aneurysm. A coronary artery aneurysm was defined as having a lumen diameter (inner border to inner border) of $\geq$3 mm in KD cases less than 5 years old and $\geq$4 mm in cases less than 5 years old, and giant aneurysm was defined as a lumen diameter of $\geq$8 mm for any one echocardiography. We took nasopharyngeal swabs and throat swabs from KD cases on the 1st day of hospitalization. These swabs were processed for both viral isolation and polymerase chain reaction (PCR) for various viruses.

Enrollment of control participants

For the healthy control group, we enrolled children who were age- and sex-matched with the KD cases, and who did not have preceding illness for the 2 weeks prior to enrollment. The preceding illness included sore throat, rash, fever, conjunctivitis, cough, rhinorrhea, abdominal pain, and diarrhea. These children were kindergarteners or children who visited our baby wellness clinics for vaccination. Informed consent was obtained from parents of all children in the control group. We also took throat swabs and nasopharyngeal swabs from the control children for viral isolation and viral PCR.

Laboratory methods

Virus isolation

Throat or nasopharyngeal swabs were submitted for virus isolation. Samples were inoculated into human embryonic fibroblast, LLC-MK2, Hep-2, and rhabdomyosarcoma cell cultures. When a cytopathic effect involved more than 50% of the cell monolayer, cells were scraped and subjected to indirect fluorescent antibody staining with specific antibodies or typed by specific methods according to the suspected types of viruses.

Molecular diagnosis for viruses

RNA and DNA extraction from throat swabs, and nasopharyngeal swabs were performed using MagNA Pure LC 2.0 System and MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche Applied Science, Roche Diagnostics, Indianapolis, IN, USA). The primers and probes for enterovirus, adenovirus, influenza B, rhinovirus, metapneumovirus real-time

PCR, and coronavirus PCR are presented in Table 1. Primers and probes for pan-enterovirus were selected based on highly conserved regions in the 5′-untranslated region of the enterovirus genome, and design of primers of other viruses are also based on their most conserved regions. The detection limitation of each virus was 100 copies for enterovirus, 100 for adenovirus, 60 for influenza B virus, 50 for rhinovirus, 50 for metapneumovirus, and 10,000 for coronavirus.

If the samples had positive viral isolation or PCR, further molecular typing was done. The detailed method of the viral molecular typing is in the Supplementary Material online.

Ethics approval

This study was conducted in Taiwan only and institutional review board (IRB) approval was obtained from National Taiwan University Hospital (IRB number 9361700624). Written informed consent was obtained from the parents of all participants.

Table 1 Primers and probes for pan-enterovirus, pan-adenovirus, pan-coronavirus, metapneumovirus, rhinovirus, and influenza B PCR.

Primer or probe	Sequence
Pan-enterovirus	
Forward primer	5′-TCCTCCGGCCCCTGAATG
Reverse primer	5′-AATTGTCACCATAAGCAGCCA
PanEV probe (TaqMan)	6FAM-AACCGACTACTTTGGGTGTC CGTGTTTCXT-PH
Pan-adenovirus	
Forward primer	5′-GCCACGGTGGGGTTTCTAAACTT-3′
Reverse primer	5′-GCCCCAGTGGTCTTACATGCACATC-3′
Pan-adenovirus probe (TaqMan)	6FAM-TGCACCAGACCCGGGCTCAGG TACTCCGA -TMR
Influenza B	
Forward primer	5′-AAATACGGTGGATTAAATAAAAGCAA-3′
Reverse primer	5′-CCAGCAATAGCTCCGAAGAAA-3′
Probe (TaqMan)	6FAM-CACCCATATTGGGCAATTTCCTA TGGC-TMR
Human rhinovirus	
Forward primer	5′-GACARGGTGTGAAGASYC-3′
Reverse primer	5′-CAAAGTAGTYGGTCCCRTCC-3′
HRV probe (TaqMan)	6FAM-TCCTCCGGCCCCTGAATGYGGC TAA-BHQ1
Human metapneumovirus	
Forward primer	5′-CATCAGGTAATATCCCACAAAATCAG-3′
Reverse primer	5′-GTGAATATTAAGGCACCTACACATA ATAARA-3′
HMPV probe (TaqMan)	6FAM-TCAG+CAC+CAGA+CACAC-BBQ
Pan-coronavirus RT-PCR	
Forward primer	5′-ACWCARHTVAAYYTNAARTAYGC-3’
Reverse primer	5′-TCRCAYTTDGGRTARTCCCA-3’
Pan-coronavirus semi-nested PCR	
Forward primer	5′-ACWCARHTVAAYYTNAARTAYGC-3′
Reverse primer	5′-CCAVCCRCCRTARAAYTT-3′

PCR = polymerase chain reaction; TaqMan = Taq polymerase plus PacMan principle.

Statistical analysis

The χ^2 test was used to compare the rates of viral isolation and PCR of various viruses between KD cases and the control children. A p *value* < 0.05 was considered statistically significant.

Results

Demographics of KD and control cases

In total, 226 KD cases as well as 226 age- and sex-matched control children were enrolled. The demographic characteristics of the KD cases and the control children are shown in Table 2. The mean age of KD cases was 2.07 ± 1.76 years, the median (range) was 1.57 (0.12—9.43) and the male to female ratio was 1.43 (133 to 93). Their age distribution is shown in Figure 1; about 62% were younger than 2 years old. The demographic characteristics of the control children were comparable to those of the KD cases.

Clinical manifestations of KD cases

Table 3 shows the clinical manifestations. Their mean (SD) fever duration was 7.5 (2.4) days with mean peak temperature of 39.7°C. For the typical clinical features of KD, rash was found in 92% of the cases, BCG scar erythema and induration in 44%, palm and/or sole erythema and induration in 72%, desquamation in 96% (96% of periungual desquamation and 24% of peri-anal desquamation) and bulbar conjunctivitis in 97%, red lip with fissure and/or strawberry tongue in 95%, and neck lymphadenopathy in 40% of cases. KD cases also had other clinical features including cough (69%), rhinorrhea (58%), and diarrhea (45%). During the acute stage, 14 (6.2%) children required intravenous immunoglobulin retreatment, 116 (51%) patients had coronary arterial lesions, and 28 (12%) patients had coronary arterial aneurysm.

For the contact history and the rate of household transmission, 60.8% of the cases had positive contact history: 51.7% of cases had contact with ill household members and 9.1% had positive contact with extra-familial ill people 1—10 days prior to their KD illness. In 129 (57%) of the 226 families, at least one of the other family members had an illness after the onset of disease in the KD cases.

Table 2 Demographic characteristics of KD cases and control children.

	KD cases (N = 226)	Control children (N = 226)	p
Age (y)			
Median (range)	1.57 (0.12—9.43)	1.49 (0.05—6.58)	0.73
Mean (SD)	2.07 (±1.76)	2.01 (±1.77)	0.72
Sex			
Male/Female	133/93 (1.43)	126/100 (1.26)	0.57

KD = Kawasaki disease.

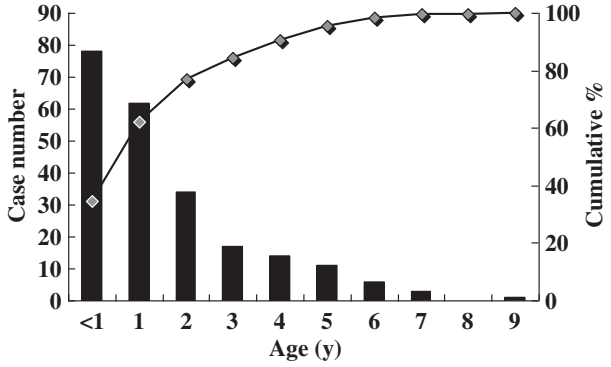

Figure 1 Age-specific case number and cumulative percentage of cases with Kawasaki disease.

Viral workup

Table 4 shows the results of viral isolation and Table 5 shows the results of viral PCR between the KD cases and the control participants. KD cases had significantly higher rates of viral isolation (7.5% vs. 2.2%, $p = 0.02$) than the control children. They also had significantly higher positive rates of PCR (50.4% vs. 16.4%, $p < 0.001$) for various viruses including enteroviruses (16.8% vs. 4.4%, $p < 0.001$), adenoviruses (8.0% vs. 1.8%, $p = 0.007$), rhinoviruses (26.5% vs. 9.7%, $p < 0.001$), and pan-coronaviruses (7.1% vs. 0.9%, $p = 0.003$). The overall results of combined viral isolation and PCR are shown in Table 6.

Table 3 Clinical manifestations of KD cases.

Manifestations	KD cases ($N = 226$)
Peak body temperature, mean (SD) °C	39.7 (0.6)
Duration of fever, mean (SD) (d)	7.5 (2.4)
Rash	208 (92)
BCG scar erythema and induration	99 (44)
Palm and/or sole erythema and induration	162 (72)
Desquamation	217 (96)
Periungual desquamation	216 (96)
Peri-anal desquamation	55 (24)
Bulbar conjunctivitis	219 (97)
Red lip with fissure and/or strawberry tongue	215 (95)
Neck lymphadenopathy	91 (40)
Others	
Cough	157 (69)
Rhinorrhea	130 (58)
Diarrhea	102 (45)
Coronary arterial lesions[a]	116 (51)
Coronary arterial aneurysm[b]	28 (12)

Data are presented as *n* (%), unless otherwise indicated.
KD = Kawasaki disease; SD = standard deviation.
[a] Coronary arterial lesions were defined as coronary arterial dilatation/ectasia, aneurysm, increased echogenicity or irregularity, and coronary artery aneurysm.
[b] A coronary artery aneurysm was defined as having a lumen diameter (inner border to inner border) of ≥3 mm in KD cases <5 years old and ≥4 mm in cases ≥5 years old.

Table 4 Viral isolation between KD cases and control children.

	KD cases ($N = 226$)	Control children ($N = 226$)	p
Positive viral isolation[a]	17 (7.5)	5 (2.2)	0.02
Specific virus			
Enteroviruses	4 (1.8)	3 (1.3)	0.99
Adenoviruses	7 (3.1)	2 (0.9)	0.19
Influenza A	2 (0.9)	0 (0)	0.48
Para-influenza type 3	3 (1.3)	0 (0)	0.25

Data are presented as *n* (%).
KD = Kawasaki disease.
[a] Herpes simplex virus and cytomegalovirus are considered latent viruses and not included in positive viral isolation.

Table 5 Viral PCR results between KD cases and control children.

	KD cases ($N = 226$)	Control children ($N = 226$)	p
Any positive	114 (50.4)	37 (16.4)	<0.001
Enterovirus	38 (16.8)	10 (4.4)	<0.001
Adenovirus	18 (8.0)	4 (1.8)	0.007
Influenza B	2 (0.9)	0 (0)	0.48
Human rhinovirus	60 (26.5)	22 (9.7)	<0.001
Human metapneumovirus	5 (2.2)	0 (0)	0.08
Coronavirus	16 (7.1)	2 (0.9)	0.003

Data are presented as *n* (%).
KD = Kawasaki disease.

As for further typing, only one case of echovirus 6 and one case of EV71 were identified among the 40 enteroviral-positive KD cases and the other enterovirus serotyping failed due to low viral titer. For adenovirus, six cases of

Table 6 Positive rate of either viral isolation or PCR results between KD cases and control children.[a]

	KD cases ($N = 226$)	Control children ($N = 226$)	p
Any positive	119 (52.7)	37 (16.4)	<0.001
Enterovirus	40 (17.7)	10 (4.4)	<0.001
Adenovirus	18 (8.0)	4 (1.8)	0.007
Human rhinovirus	60 (26.5)	22 (9.7)	<0.001
Human metapneumovirus	5 (2.2)	0 (0)	0.08
Coronavirus	16 (7.1)	2 (0.9)	0.003
Influenza A	2 (0.9)	0 (0)	0.48
Influenza B	**2 (0.9)**	**0 (0)**	**0.48**
Para-influenza type 3	3 (1.3)	0 (0)	0.25

Data are presented as *n* (%).
KD = Kawasaki disease.
[a] Herpes simplex virus and cytomegalovirus are considered latent viruses and not considered as positive.

serotype 3, five cases of serotype 5, three cases of serotype 2, one case of serotype 1, and one case of serotype 4 were identified in KD cases, whereas two cases of adenovirus serotype 2, one case of serotype 3, and one case of serotype 1 were identified in the control children. For coronavirus, 12 cases of human coronavirus NL63, three cases of human coronavirus 229E, and one case of human coronavirus OC43 were identified in KD cases whereas two of human coronavirus 229E were identified in the control children. For rhinovirus, 36 serotypes were identified and type C was the most common (7 cases) in the 60 rhinovirus-positive KD cases whereas 14 serotypes were identified and the Antwerp RV 98/99 type was the most common (5 cases) among the 22 rhinovirus-positive control children.

Overall, 119 (52.7%) KD cases had positive viral results by either viral isolation or PCR. However, KD cases with positive viral results did not have significantly higher percentages of needing intravenous immunoglobulin retreatment (4% vs. 8%, $p = 0.18$), coronary arterial lesions (53% vs. 50%, $p = 0.70$), or coronary arterial aneurysm (11% vs. 14%, $p = 0.45$) than KD cases without positive viral results.

Discussion

This was a prospective study to investigate the association of common viruses with Kawasaki disease. We found that cases of KD frequently had a cough (69%), rhinorrhea (58%), and diarrhea (51%) in addition to the typical symptoms of KD; several common respiratory viruses were also more frequently detected in cases of KD than in the control children. We propose that heterogeneous infectious agents, such as common viruses found in our study, may trigger Kawasaki disease in young children with certain genetic backgrounds or susceptibility.

The leading theory of KD etiology is that a ubiquitous infectious etiologic agent, that usually results in asymptomatic or mild infection in most people, causes KD in a small subset of genetically predisposed children. In our study, approximately 60% of KD cases had a preceding contact history with people of febrile, respiratory, or gastrointestinal illness, and KD cases frequently had cough (69%), rhinorrhea (58%), and diarrhea (45%), which supported certain kinds of viral infections. A winter—spring predominance of KD cases in non-temperate climates also suggests the association of KD with some kinds of viral infections,[11] particularly a respiratory infection, and this theory is supported by the two articles which reported a preceding history of respiratory illness in some KD patients.[7,8] The other infectious evidence of Kawasaki disease includes geographic clustering, family clustering, high association between Kawasaki disease and infectious disease surveillance, and age distribution, with the highest incidence rates among children aged from 6 months to 2 years old who have low maternal antibodies and are most susceptible to infections in general.[11—14]

Many studies worked on a certain single pathogen to be associated with KD. Various infectious agents including bacterial (*Staphylococcus aureus*, group A *Streptococcus*, *Yersinia pseudotuberculosis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), viral (parvovirus B19, Epstein—Barr virus, CMV, HHV6, retrovirus, rotavirus, parainfluenza virus, New Haven coronavirus, measles, chickenpox, dengue fever), *Chlamydiae pneumoniae*, *Mycoplasma pneumoniae*, *Rickettsial* organisms, and so-called KD agent, a viral etiology characterized by intracytoplasmic inclusion bodies, have been found to be associated with KD.[15—39] However, at present, links between any of these individual agents and KD have not been irrefutably established.

Although KD had temporal clustering, different seasonality was found in different countries. For example, studies from Europe and Canada reported a higher incidence in winter,[40] whereas Taiwan and Korea have the highest incidence rates of KD during the summer,[11,41] Beijing and Hong Kong in the spring and summer, and Japan in January and summer.[3,42,43] Such seasonality and temporal clustering of KD suggests that different infectious diseases in different countries might trigger this clustering presentation. In the summer, enterovirus infection was one of the most common infections in young children in Taiwan. We also detected enterovirus most frequently in KD cases, which links enterovirus with KD in the summer. Other respiratory viruses, such as adenoviruses, may play an important role during other seasons because adenoviruses circulate all year-round in Taiwan. We proposed that it was not the same infectious etiology, but rather heterogeneous infectious agents in different areas and different seasons, which trigger KD; there was no single pathogen reported to be associated with KD worldwide. That is to say, different pathogens might be responsible for KD in different countries or different seasons. This may explain why no single pathogen was consistently found in cases with Kawasaki disease. For example, Jordan-Villegas et al[44] reported that 8.8% of KD patients had documented respiratory viral infections including rhinovirus, adenovirus, influenza, parainfluenza, and respiratory syncytial virus. A recent article also reported a case of KD associated with parainfluenza type 3 viral infection,[45] and another article reported adenovirus detection in some KD cases.[46] However, Kim et al[47] reported that there was no significant association between the presence of any of the 15 respiratory viruses and the incidence of KD. New tests or techniques for specific microorganisms may help us find the etiology of KD.[48,49]

In conclusion, we found that common respiratory viruses, such as enteroviruses, adenoviruses, rhinoviruses, and coronaviruses, were associated with KD. Heterogeneous infectious etiologies may be responsible for KD in different countries as well as during different seasons.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2013.12.008.

References

1. Kawasaki T. Pediatric acute febrile mucocutaneous lymph node syndrome with characteristic desquamation of fingers and toes: my clinical observation of fifty cases. *Japanese J of Allergy* 1967;**178**:178—222.
2. Yanagawa H, Yashiro M, Nakamura Y, Kawasaki T, Kato H. Epidemiologic pictures of Kawasaki disease in Japan: from the

nationwide incidence survey in 1991 and 1992. *Pediatrics* 1995; **95**:475—9.
3. Du ZD, Zhao D, Du J, Zhang YL, Lin Y, Liu C, et al. Epidemiologic study on Kawasaki disease in Beijing from 2000 through 2004. *Pediatr Infect Dis J* 2007;**26**:449—51.
4. 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.
5. Belay ED, Holman RC, Maddox RA, Foster DA, Schonberger LB. Kawasaki syndrome hospitalizations and associated costs in the United States. *Public Health Rep* 2003;**118**:464—9.
6. Gardner-Medwin JM, Dolezalova P, Cummins C, Southwood TR. Incidence of Henoch—Schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. *Lancet* 2002;**360**:1197—202.
7. Park YW, Park IS, Kim CH, Ma JS, Lee SB, Kim CH, et al. Epidemiologic study of Kawasaki disease in Korea, 1997—1999: comparison with previous studies during 1991—1996. *J Korean Med Sci* 2002;**17**:453—6.
8. Royle JA, Williams K, Elliott E, Sholler G, Nolan T, Allen R, et al. Kawasaki disease in Australia, 1993—95. *Arch Dis Child* 1998;**78**:33—9.
9. Schiller B, Fasth A, Bjorkhem G, Elinder G. Kawasaki disease in Sweden: incidence and clinical features. *Acta Paediatr* 1995; **84**:769—74.
10. Salo E. Kawasaki disease in Finland in 1982—1992. *Scand J Infect Dis* 1993;**25**:497—502.
11. Chang LY, Chang IS, Lu CY, Chiang BL, Lee CY, Chen PJ, et al. Epidemiological features of Kawasaki disease in Taiwan from 1996 to 2002. *Pediatrics* 2004;**114**:e678—82.
12. Yanagawa H, Nakamura Y, Ojima T, Yashiro M, Tanihara S, Oki I. Changes in epidemic patterns of Kawasaki disease in Japan. *Pediatr Infect Dis J* 1999;**18**:64—6.
13. Nakamura Y, Yashiro M, Yanagawa H. Validity of the infectious disease surveillance system on comparison of nationwide surveys of Kawasaki disease during a 10-year period. *Nippon Koshu Eisei Zasshi* 2000;**47**:1029—35.
14. Nakamura Y, Yanagawa I, Kawasaki T. Temporal and geographic clustering of Kawasaki disease in Japan. *Prog Clin Biol Res* 1987;**250**:19—32.
15. Uchiyama T, Kato H. The pathogenesis of Kawasaki disease and superantigens. *Jpn J Infect Dis* 1999;**52**:141—5.
16. Schrag SJ, Besser RE, Olson C, Burns JC, Arguin PM, Gimenez-Sanchez F, et al. Lack of association between Kawasaki syndrome and Chlamydia pneumoniae infection: an investigation of a Kawasaki syndrome cluster in San Diego County. *Pediatr Infect Dis J* 2000;**19**:17—22.
17. Chua PK, Nerurkar VR, Yu Q, Woodward CL, Melish ME, Yanagihara R. Lack of association between Kawasaki syndrome and infection with parvovirus B19, human herpesvirus 8, TT virus, GB virus C/hepatitis G virus or Chlamydia pneumoniae. *Pediatr Infect Dis J* 2000;**19**:477—9.
18. Bell DM, Brink EW, Nitzkin JL, Hall CB, Wulff H, Berkowitz ID, et al. Kawasaki syndrome: description of two outbreaks in the United States. *N Engl J Med* 1981;**304**:1568—75.
19. Dean AG, Melish ME, Hicks R, Palumbo NE. An epidemic of Kawasaki syndrome in Hawaii. *J Pediatr* 1982;**100**:552—7.
20. Keren G, Barzilay Z, Alpert G, Spirer Z, Danon Y. Mucocutaneous lymph node syndrome (Kawasaki disease) in Israel. A review of 13 cases: is pseudomonas infection responsible? *Acta Paediatr Scand* 1983;**72**:455—8.
21. Hansen RC. Staphylococcal scalded skin syndrome, toxic shock syndrome, and Kawasaki disease. *Pediatr Clin North Am* 1983; **30**:533—44.
22. Reller M, DeCristofaro J, Schwartz DC. Coronary aneurysms in a patient with atypical Kawasaki syndrome and a streptococcal infection. *Pediatr Cardiol* 1984;**5**:205—7.
23. Umehara K, Kuno-Sakai H, Iwasaki H, Takesue R, Hoshi N, Furukawa T, et al. Trial of isolation of a virus from sera of patients with Kawasaki disease. *Tokai J Exp Clin Med* 1986;**11**:19—21.
24. Klein BS, Rogers MF, Patrican LA, White MC, Burgdorfer W, Schell WL, et al. Kawasaki syndrome: a controlled study of an outbreak in Wisconsin. *Am J Epidemiol* 1986;**124**:306—16.
25. Kikuta H, Taguchi Y, Tomizawa K, Kojima K, Kawamura N, Ishizaka A, et al. Epstein—Barr virus genome-positive T lymphocytes in a boy with chronic active EBV infection associated with Kawasaki-like disease. *Nature* 1988;**333**:455—7.
26. Rauch AM. Kawasaki syndrome: issues in etiology and treatment. *Adv Pediatr Infect Dis* 1989;**4**:163—82.
27. Okano M, Luka J, Thiele GM, Sakiyama Y, Sakiyama Y, Matsumoto S, et al. Human herpesvirus 6 infection and Kawasaki disease. *J Clin Microbiol* 1989;**27**:2379—80.
28. Enders G, Biber M, Meyer G, Helftenbein E. Prevalence of antibodies to human herpesvirus 6 in different age groups, in children with exanthema subitum, other acute exanthematous childhood diseases, Kawasaki syndrome, and acute infections with other herpesviruses and HIV. *Infection* 1990;**18**:12—5.
29. Marchette NJ, Melish ME, Hicks R, Kihara S, Sam E, Ching D. Epstein—Barr virus and other herpesvirus infections in Kawasaki syndrome. *J Infect Dis* 1990;**161**:680—4.
30. Okano M, Thiele GM, Sakiyama Y, Matsumoto S, Purtilo DT. Adenovirus infection in patients with Kawasaki disease. *J Med Virol* 1990;**32**:53—7.
31. Akiyama T, Osawa N, Shimanuki K, Yashiro K, Oyake T. Possible role of Streptococcus pyogenes in mucocutaneous lymph node syndrome. XII. Variable responses of platelets in MCLS seem to be explainable by streptococcal pyrogenic exotoxin. *Acta Paediatr Jpn* 1990;**33**:20—6.
32. Kikuta H, Matsumoto S, Osato T. Kawasaki disease and Epstein-Barr virus. *Acta Paediatr Jpn* 1991;**33**:765—70.
33. Lin CY, Chen IC, Cheng TI, Liu WT, Hwang B, Chiang BN. Virus-like particles with reverse transcriptase activity associated with Kawasaki disease. *Med Virol* 1992;**38**:175—82.
34. Abinun M, Cant AJ. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. *Lancet* 1994; **343**:300.
35. Anderson DG, Warner G, Barlow E. Kawasaki disease associated with streptococcal infection within a family. *J Paediatr Child Health* 1995;**31**:355—7.
36. Morita A, Imada Y, Igarashi H, Yutsudo T. Serologic evidence that streptococcal superantigens are not involved in the pathogenesis of Kawasaki disease. *Microbiol Immunol* 1997;**41**: 895—900.
37. Barton M, Melbourne R, Morais P, Christie C. Kawasaki syndrome associated with group A streptococcal and Epstein—Barr virus co-infections. *Ann Trop Paediatr* 2002;**22**:257—60.
38. Kafetzis DA, Maltezou HC, Constantopoulou I, Antonaki G, Liapi G, Mathioudakis I. Lack of association between Kawasaki syndrome and infection with *Rickettsia conorii, Rickettsia typhi, Coxiella burnetii* or *Ehrlichia phagocytophila* group. *Pediatr Infect Dis J* 2001;**20**:703—6.
39. Rowley AH, Baker SC, Shulman ST, Fox LM, Takahashi K, Garcia FL, et al. Cytoplasmic inclusion bodies are detected by synthetic antibody in ciliated bronchial epithelium during acute Kawasaki disease. *J Infect Dis* 2005;**192**:1757—66.
40. Lynch M, Holman RC, Mulligan A, Belay ED, Schonberger LB. Kawasaki syndrome hospitalizations in Ireland, 1996 through 2000. *Pediatr Infect Dis J* 2003;**22**:959—63.
41. Park YW, Han JW, Park IS, Kim CH, Cha SH, Ma JS, et al. Kawasaki disease in Korea, 2003—2005. *Pediatr Infect Dis J* 2007; **26**:821—3.
42. Ng YM, Sung RY, So LY, Fong NC, Ho MH, Cheng YW, et al. Kawasaki disease in Hong Kong, 1994 to 2000. *Hong Kong Med J* 2005;**11**:331—5.

43. Burns JC, Cayan DR, Tong G, Bainto EV, Turner CL, Shike H, et al. Seasonality and temporal clustering of Kawasaki syndrome. *Epidemiology* 2005;**16**:220—5.
44. Jordan-Villegas A, Chang ML, Ramilo O, Mejías A. Concomitant respiratory viral infections in children with Kawasaki disease. *Pediatr Infect Dis J* 2010;**29**:770—2.
45. Moreira A, Leite I, Baptista A, Osório Ferreira E. Kawasaki disease associated with parainfluenza type 3 virus infection. *Acta Dermatovenerol Croat* 2010;**18**:120—3.
46. Jaggi P, Kajon AE, Mejias A, Ramilo O, Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? *Clin Infect Dis* 2013;**56**:58—64.
47. Kim JH, Yu JJ, Lee J, Kim MN, Ko HK, Choi HS, et al. Detection rate and clinical impact of respiratory viruses in children with Kawasaki disease. *Korean J Pediatr* 2012;**55**:470—3. 48.
48. Lu CY, Chang LY, Chen PJ, Xia NS, Shao PL, Huang LM. A highly specific ELISA for diagnosis of 2009 influenza A (H1N1) virus infections. *J Formosan Med Assoc* 2012;**111**:693—7.
49. Tseng YT, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18—40 years in Taiwan. *J Formosan Med Assoc* 2012;**111**:431—8.