Pediatrics and Neonatology (2013) 54, 43—48

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.pediatr-neonatol.com

ORIGINAL ARTICLE

Reaction at the Bacillus Calmette—Guérin Inoculation Site in Patients with Kawasaki Disease

Chi-Chieh Lai [a,b], Pi-Chang Lee [b,c], Chih-Chien Wang [a], Be-Tau Hwang [c,d], C.C. Laura Meng [b], Ming-Chih Tsai [a,*]

[a] Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[b] Division of Pediatric Cardiology, Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan, ROC
[c] School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC
[d] Department of Pediatrics, Taipei City Hospital, Zhongxiao Branch, Taipei, Taiwan, ROC

Received Sep 20, 2011; received in revised form Dec 5, 2011; accepted May 23, 2012

Key Words
bacillus Calmette—Guérin; diagnosis; Kawasaki disease

Background: The bacillus Calmette—Guérin (BCG) reaction is not included in the classical clinical criteria for Kawasaki disease (KD). However, a reaction at the BCG inoculation site has been mentioned among the "other clinical findings" that are present in about 30—50% of KD patients. The objective of this study was to investigate the clinical characteristics of KD patients with reactions at the BCG inoculation site.
Methods: A retrospective study of all patients diagnosed with KD between September 2000 and August 2010 was performed. The clinical presentations, laboratory results, treatment outcomes, and coronary artery abnormalities in the BCG-reactive [BCG(+)] and BCG-nonreactive [BCG(−)] groups were analyzed and compared.
Results: In total, 145 patients with KD diagnosed at our institution were included; 46 (31.7%) had a reaction at the BCG inoculation site. The BCG(+) group was younger than the BCG(−) group. Laboratory results showed higher white blood cell counts, platelet counts, and serum potassium levels, and lower low-density lipoprotein levels in the BCG(+) group. The BCG(+) group had a shorter fever duration before intravenous immunoglobulin treatment and a shorter total fever duration than the BCG(−) group. Multivariable logistic regression analysis showed that the age at diagnosis was the only factor significantly associated with a reaction at the BCG inoculation site in KD patients.
Conclusions: In countries with a national BCG vaccination program, a reaction at the BCG inoculation site could be a useful and early diagnostic sign of KD among younger patients, especially those younger than 6 months.

* Corresponding author. Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, 325 Cheng-Kung Road, Section 2, Neihu, Taipei 114, Taiwan, ROC.
E-mail address: m850902@yahoo.com.tw (M.-C. Tsai).

1875-9572/$36
http://dx.doi.org/10.1016/j.pedneo.2012.10.003

1. Introduction

Kawasaki disease (KD), an acute febrile, self-limiting vasculitis of unknown etiology that occurs predominantly in children younger than 5 years, was first described by Tomisaku Kawasaki in 1967 in Japan.[1] The clinical criteria include fever for 5 days or more, and the following five principal clinical symptoms: polymorphous exanthema, nonpurulent bilateral conjunctivitis, changes in the lips or oral cavity, changes in the peripheral extremities, and a cervical lymph node >1.5 cm in diameter. The diagnosis is made when the child has experienced fever for 5 days or more, has four of the other five signs, and shows no evidence of another disease with similar clinical features.[2] In addition to the diagnostic criteria, a broad range of nonspecific clinical features can be observed, including irritability, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, gall bladder hydrops, arthralgia, arthritis, hypoalbuminemia, liver function impairment, sterile pyuria, and a reaction at the bacillus Calmette–Guérin (BCG) inoculation site.[2,3]

Patients with KD who displayed erythema at the BCG inoculation site were first described by Kawasaki in 1970.[4] A reaction at the BCG site is not included in the classical clinical diagnostic criteria for KD, published by the American Heart Association. However, a reaction at the BCG inoculation site is mentioned among the "other clinical findings" that are present in about 30–50% of KD patients.[2,3,5,6] The prevalence of a reaction at the BCG inoculation site is even higher than the incidence of cervical lymphadenopathy among patients with complete KD aged 3–20 months.[6] The reason for this reaction in children with KD is still unclear. However, previous studies have suggested that cross-reactivity occurs between specific epitopes on the mycobacterial 65-kDa heat-shock protein and the human homologue, heat-shock protein 65.[7,8]

The associations between the reaction at the BCG inoculation site and the principal clinical signs, laboratory results, treatment outcome, and coronary artery involvement in KD patients are unclear. The purpose of this study was to investigate the clinical characteristics of KD patients with a reaction at the BCG inoculation site.

2. Methods

The medical records of 145 KD patients who were treated in our institution from September 2000 to August 2010 were reviewed. The reaction at the BCG inoculation site, defined as any redness, induration, or crust formation, was recorded precisely before and during hospitalization in all of these patients. All the patients with KD had received a BCG vaccination before 1 month of age. We divided these patients into two groups according to the reaction at the BCG inoculation site. The clinical manifestations of KD, laboratory results, coronary artery abnormalities, and treatment outcomes of the two groups were analyzed and compared. The study was approved by the hospital institutional review board, and the requirement for individual consent was waived for this retrospective study.

The diagnosis of KD was made in accordance with the clinical criteria published by the American Heart Association. Incomplete KD is defined as an unexplained fever for 5 days or more associated with two or three of the principal clinical features of KD but with cardiac or coronary artery involvement.[2] The duration of the febrile period was counted from the onset of fever until intravenous immunoglobulin (IVIG) treatment had started (pre-IVIG fever) or the fever had subsided completely (total fever). The Japanese Ministry of Health criteria classify coronary arteries as abnormal if the internal lumen diameter is >3 mm in children younger than 5 years or >4 mm in children 5 years or older; if the internal diameter of the segment is ≥1.5 times greater than that of the adjacent segment; or if the coronary lumen is clearly irregular.[5]

High-dose IVIG (2 g/kg delivered in a single dose or 1 g/kg given for 2 days) and aspirin (60 mg/kg per day) were given during the acute stage when the diagnosis had been confirmed. After the fever had subsided for 48 hours, we reduced the aspirin dose to 3–5 mg/kg per day to inhibit platelet aggregation. Failure of the body temperature to normalize within 48 hours of treatment with the first dose of IVIG was defined as resistant fever, which was treated with a second dose of IVIG at 2 g/kg. Failure of the second IVIG treatment prompted treatment with a third dose of IVIG. Low-dose aspirin was stopped 3 months later if the patient showed no coronary artery involvement on echocardiography. We prescribed an alternative platelet aggregation inhibitor (dipyridamole, 5 mg/kg per day) in patients with a glucose-6-phosphate dehydrogenase deficiency. If there was echocardiographic evidence of coronary involvement, aspirin was continued for as long as the abnormality persisted.

All parametric data are expressed as mean ± standard deviation or percentage as appropriate. Continuous data were compared using the Student t test. Significance of differences in the percentages and rates of incidence between the two groups were compared using the χ^2 test with Yates' correction. Fisher's exact probability test was applied when examining variables with a low incidence. All parameters were initially examined by means of univariate analysis; parameters with $p < 0.05$ as statistical significance were introduced into the multivariate analysis, in which all variables were continuous data. Binary logistic regression and odds ratios were implemented to estimate possible correlations between the factors analyzed and the incidence of a reaction at the BCG inoculation site in KD patients. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical evaluations. A p value <0.05 was considered statistically significant.

3. Results

Of the 145 KD patients reviewed, 46 (31.7%) had a reaction at the BCG inoculation site [BCG(+) group], whereas 99 patients (68.3%) had no reaction at the BCG inoculation site [BCG(−)]. All the KD patients with a reaction at the BCG inoculation site were younger than 20 months of age (range, 3–20 months). The age-specific percentage of KD patients who had a reaction at the BCG inoculation site was highest in patients younger than 6 months of age (17 of 25

patients, 68.0%; Figure 1). In the BCG(+) group, the percentage of male patients was significantly higher than that of female patients (67.4% vs. 32.6%, respectively, $p = 0.018$).

Table 1 summarizes the clinical manifestations and laboratory results for these patients. The BCG(+) group was younger than the BCG(−) group (9.0 ± 4.9 months vs. 29.0 ± 25.3 months, respectively, $p < 0.001$). Patients in the BCG(+) group had higher white blood cell counts, platelet counts, and serum potassium levels, and lower low-density lipoprotein levels. The BCG(+) group had lower concentrations of hemoglobin, serum C-reactive protein, and serum cholesterol, higher serum sodium level and total cholesterol concentration, and higher incidence of pyuria compared with the BCG(−) group, although these differences were not significant. The major clinical manifestations did not differ significantly between the BCG(+) and BCG(−) groups. The BCG(+) group had a shorter pre-IVIG fever duration than did the BCG(−) group (5.9 ± 1.9 vs. 7.5 ± 3.0 days, respectively, $p = 0.001$) and a shorter total fever duration (7.2 ± 2.0 vs. 8.5 ± 3.0 days, respectively, $p = 0.008$). However, there was no difference between the two groups in the fever duration of the post-IVIG treatment or the length of hospital stay.

Six patients (13.0%) were diagnosed with incomplete KD in the BCG(+) group, and 14 patients (14.1%) had incomplete KD in the BCG(−) group; this difference was not significant. In the BCG(+) group, four patients had persistent fever after the first dose of IVIG. Three responded to a second dose of IVIG, and the remaining patient required a third dose of IVIG. In the BCG(−) group, six patients had persistent fever after the first dose of IVIG was administered. Three responded to a second dose, whereas the other three patients required a third dose of IVIG. There was no significant difference between the two groups in their requirement for IVIG retreatment. Two patients in the BCG(+) group and seven patients in the BCG(−) group had coronary artery abnormalities, but this difference was not significant.

To investigate the association between a reaction at the BCG inoculation site and each major clinical manifestation of KD in KD patients of different ages, we compared the prevalence of a reaction at the BCG inoculation site and the major clinical manifestations of KD in the patients younger and older than 2 years. KD patients younger than 2 years had a lower prevalence of cervical lymphadenopathy and a higher frequency of a reaction at the BCG inoculation site than did KD patients aged 2 years or older (Table 2). The prevalence of a reaction at the BCG inoculation site among KD patients younger than 2 years was also higher than the incidence of cervical lymphadenopathy.

Several variables, including those that differed significantly between the BCG(+) and BCG(−) groups (Table 1), were tested in multivariable logistic regression analysis (Table 3). The age at onset had an odds ratio of 0.830 (95% confidence interval = 0.734–0.938, $p = 0.003$), indicating that the prevalence of a reaction at the BCG inoculation site decreased with increasing age in KD patients. The two groups did not differ significantly in terms of the other variables tested.

4. Discussion

In our study, a reaction at the BCG inoculation site developed more frequently in younger KD patients, especially in those aged less than 6 months. No KD patient with a reaction at the BCG inoculation was older than 20 months. This finding is similar to that of a previous study by Takayama et al, who reported that 36% of KD patients developed erythema at the BCG inoculation site, with the highest rate (88%) of reaction observed in KD patients 4–6 months after their BCG inoculation.[9] None of their KD patients showed a reaction at the BCG inoculation site 37 months or more after their BCG inoculations.[9] It appears that the prevalence of this reaction in KD patients declines with time after the BCG vaccination.

The marked leukocytosis and thrombocytosis we observed in the KD patients with a reaction at the BCG inoculation site suggest a more severe inflammatory process. Similar results have been reported in several earlier studies, in which marked leukocytosis and thrombocytosis were noted in younger infants, whereas higher values for inflammatory indices were observed in older

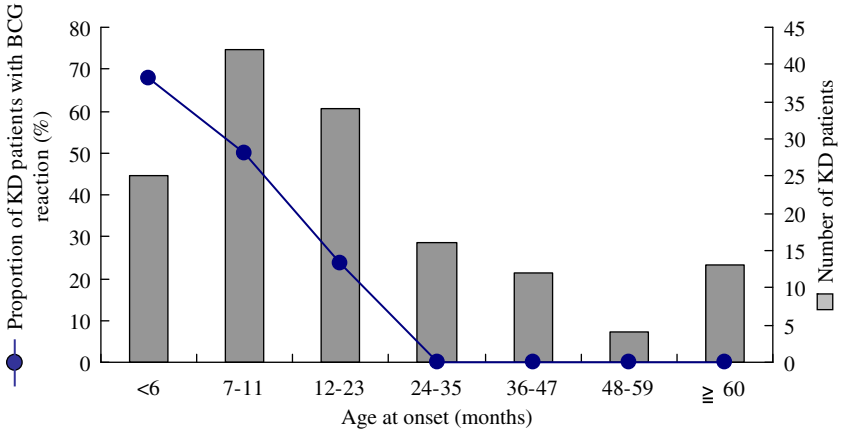

Figure 1 Age distribution of KD and age-specific rates of reaction at the BCG inoculation site among patients with KD. BCG = bacillus Calmette–Guérin; KD = Kawasaki disease.

Table 1 Comparison of the clinical manifestations and laboratory results of patients with and without a reaction at the bacillus Calmette–Guérin (BCG) inoculation site.

	BCG(+) (n = 46)	BCG(−) (n = 99)	p
Age (mo)	9.0 ± 4.9	29.0 ± 25.3	<0.001*
Male	31 (67.4)	59 (60.0)	0.502
WBC count ($\times 10^9$/L)	18.1 ± 6.8	15.2 ± 6.2	0.01*
Hb (g/L)	105.9 ± 11.4	108.6 ± 13.0	0.177
Platelets ($\times 10^9$/L)	480.5 ± 171.5	405.3 ± 183.2	0.02*
CRP (mg/L)	90.6 ± 62.9	110.7 ± 80.7	0.134
AST (U/L)	83.2 ± 125.8	86.3 ± 114.3	0.883
ALT (U/L)	59.6 ± 52.9	78.7 ± 130.2	0.340
Albumin (g/L)	38.1 ± 4.6	36.8 ± 5.8	0.312
Serum sodium (mmol/L)	137.4 ± 2.6	136.6 ± 3.3	0.150
Serum potassium (mmol/L)	4.7 ± 0.4	4.3 ± 0.6	<0.001*
Cholesterol (mmol/L)	3.28 ± 0.85	3.49 ± 0.96	0.200
Triglycerides (mmol/L)	1.63 ± 0.68	1.60 ± 0.73	0.804
HDL-C (mmol/L)	0.63 ± 0.31	0.60 ± 0.27	0.574
LDL-C (mmol/L)	1.80 ± 0.76	2.11 ± 0.80	0.029*
Pyuria, (>10 WBCs/HPF)	18 (39.1)	27 (27.2)	0.212
Major clinical manifestations			
Fever >5 d	46 (100)	99 (100)	1.000
Conjunctival injection	43 (93.5)	88 (88.9)	0.568
Skin rash	43 (93.5)	89 (89.9)	0.694
Mucosal change in the oropharynx	44 (95.7)	91 (91.9)	0.625
Change in the extremities	25 (54.3)	49 (49.5)	0.719
Cervical lymphadenopathy	13 (28.3)	40 (40.4)	0.221
Length of hospital stay (d)	5.6 ± 2.7	6.3 ± 3.5	0.232
Duration of pre-IVIG fever (d)	5.9 ± 1.9	7.5 ± 3.0	0.001*
Duration of post-IVIG fever (d)	1.3 ± 1.1	1.1 ± 0.6	0.159
Duration of total fever (d)	7.2 ± 2.0	8.5 ± 3.0	0.008*
Incomplete Kawasaki disease	6 (13.0)	14 (14.1)	0.936
Failure of the first IVIG treatment	4 (8.7)	6 (6.1)	0.824
Coronary artery abnormality	2 (4.3)	7 (7.1)	0.779
Coronary artery aneurysm	2 (4.3)	3 (3.0)	0.928

Data are expressed as means ± standard deviations or n (%).
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCG(+) = KD patients with a reaction at the BCG inoculation site; BCG(−) = KD patients without a reaction at the BCG inoculation site; CRP = C-reactive protein; Hb = hemoglobin; HDL-C = high-density lipoprotein cholesterol; HPF = high-power field; IVIG = intravenous immunoglobulin; LDL-C = low-density lipoprotein cholesterol; WBC = white blood cell.
* Statistically significant.

children.[10–12] In our study, serum potassium levels were significantly higher in the BCG(+) group than in the BCG(−) group. Serum potassium is elevated in patients with thrombocytosis because potassium is released from platelets during their coagulation.[13]

There are several possible explanations for the shorter time from disease onset to appropriate treatment in KD patients with a reaction at the BCG inoculation site. First, a reaction at the BCG inoculation site appears in the early stages of KD. An erythematous reaction at the BCG inoculation site usually appears 24–48 hours after fever onset and forms a crust shortly after the fever subsides.[9] Second, KD patients with a reaction at the BCG inoculation site visited a hospital earlier after the onset of the illness. In our study, the KD patients with a reaction at the BCG inoculation site usually visited a hospital 1–4 days after the onset of the illness.[6] Third, physicians always consider KD if the patient has a reaction at the BCG inoculation site accompanied by fever or other major signs of KD because of the higher prevalence of this reaction among patients with KD than among those with other febrile illnesses.[6] All of these factors facilitate the earlier recognition of KD and the earlier administration of the appropriate treatment in KD patients with a reaction at the BCG inoculation site.

Many studies have demonstrated that the clinical manifestations of KD vary with age, reflecting age-dependent host responses to common immunological stimuli.[12,14] Of the five major clinical diagnostic criteria for KD, all occur with equivalent frequencies at all ages, with the exception of cervical lymphadenopathy.[12,14] The prevalence of cervical lymphadenopathy is lower in young KD patients than that in older KD patients. As in our study, KD patients younger than 2 years have a lower prevalence of cervical lymphadenopathy than do KD patients aged 2 years

Table 2 Diagnostic clinical manifestations of Kawasaki disease according to age.

	<2 y (n = 100)	≥2 y (n = 45)	p
Clinical manifestations			
Conjunctival injection	92 (92)	39 (87)	0.366
Skin rash	90 (90)	42 (93)	0.755
Mucosal change in the oropharynx	94 (94)	41 (91)	0.501
Changes in the extremities	51 (51)	23 (51)	0.990
Cervical lymphadenopathy	25 (25)	28 (62)	<0.001*
Reaction at BCG inoculation site	46 (46)	0 (0)	<0.001*

Data are presented as n (%).
BCG = bacillus Calmette–Guérin.
* Statistically significant.

or older. KD patients younger than 2 years also have a higher frequency of a reaction at the BCG inoculation site than do KD patients aged 2 years or older. Furthermore, the prevalence of a reaction at the BCG inoculation site among KD patients younger than 2 years is higher than the incidence of cervical lymphadenopathy. We propose that a reaction at the BCG inoculation site may be a useful sign of KD in patients younger than 2 years because the prevalence of this reaction is high in KD patients in this age group.

Coronary artery abnormality remains a major sequela of KD. Previous studies found no association between a reaction at the BCG inoculation site and coronary artery abnormalities in KD patients.[6,15] Our study also showed a similar association insofar as the proportion of coronary artery abnormalities was lower in KD patients with a reaction at the BCG inoculation site than in those with no such reaction. However, KD patients with a reaction at the BCG inoculation site had marked leukocytosis and thrombocytosis, which are associated with coronary artery abnormalities in KD patients.[16] In these patients, the period from symptom onset to the administration of appropriate treatment was also shorter, and a shorter interval is associated with a reduced risk of coronary artery abnormality.[13,16–18] Both the timing of treatment and laboratory markers are associated with coronary artery abnormalities in KD. The actual association between coronary artery abnormalities and a reaction at the BCG inoculation site in KD patients requires further investigation.

Table 3 Multivariable logistic regression analysis of factors associated with a reaction at the BCG inoculation site in Kawasaki disease patients.

Variable	Odds ratio (95% CI)	p
Age at onset (mo)	0.830 (0.734–0.938)	0.003*
WBC count	1.000 (1.000–1.000)	0.307
Platelet count	1.000 (1.000–1.000)	0.253
Serum potassium	0.706 (0.119–4.182)	0.701
LDL	1.006 (0.982–1.030)	0.647
Duration of pre-IVIG fever	0.684 (0.286–1.636)	0.394
Duration of total fever	0.827 (0.328–2.087)	0.688

BCG = bacillus Calmette–Guérin; CI = confidence interval; IVIG = intravenous immunoglobulin; LDL = low-density lipoprotein; WBC = white blood cell.
* Statistically significant.

5. Conclusion

The diagnosis of KD is based predominantly on its clinical manifestations and the exclusion of other diseases, because no specific diagnostic test is currently available. However, the clinical manifestations of KD vary with age. In countries with a national BCG vaccination program, a reaction at the BCG inoculation site could be a useful and early diagnostic sign of KD among younger patients, especially in those younger than 6 months. Physicians should also recognize the possibility of KD in patients younger than 2 years with three or fewer of the clinical criteria for KD but with a reaction at the BCG inoculation site.

References

1. Kawasaki T, Kousaki F. Febrile oculo-oro-cutaneo-acrodesquamatous syndrome with or without acute non-suppurative cervical lymphadenitis in infancy and children: clinical observations of 50 cases. *Jpn J Allergol* 1967;**16**: 178–223 [in Japanese].
2. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004;**110**: 2747–71.
3. Wang CL, Wu YT, Liu CA, Kuo HC, Yang KD. Kawasaki disease: infection, immunity and genetics. *Pediatr Infect Dis J* 2005;**24**: 998–1004.
4. Kawasaki T. Two cases with acute febrile mucocutaneous lymph node syndrome possibly induced by vaccinia or measles vaccination. *Jpn J Pediatr* 1970;**23**:657–62 [in Japanese].
5. Research Committee on Kawasaki Disease. *Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease*. Tokyo, Japan: Japanese Ministry of Health and Welfare; 1984.
6. Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette-Guérin inoculation site. *Pediatr Infect Dis J* 2010;**29**:430–3.

7. Sireci G, Dieli F, Salerno A. T cells recognize an immunodominant epitope of heat shock protein 65 in Kawasaki disease. *Mol Med* 2000;**6**:581—90.
8. Yokota S, Tsubaki K, Kuriyama T, Shimizu H, Ibe M, Mitsuda T, et al. Presence in Kawasaki disease of antibodies to mycobacterial heat-shock protein HSP65 and autoantibodies to epitopes of human HSP65 cognate antigen. *Clin Immunol Immunopathol* 1993;**67**:163—70.
9. Takayama J, Yanase Y, Kawasaki T. A study on erythematous change at the site of the BCG inoculation. *Acta Pediatr Jpn* 1982;**86**:567—72.
10. Chang FY, Hwang B, Chen SJ, Lee PC, Meng CC, Lu JH. Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatr Infect Dis J* 2006;**25**:241—4.
11. Momenah T, Sanatani S, Potts J, Sandor GG, Human DG, Patterson MW. Kawasaki disease in the older child. *Pediatrics* 1998;**102**:e7.
12. Lee KY, Hong JH, Han JW, Lee JS, Lee BC, Burgner D. Features of Kawasaki disease at the extremes of age. *J Paediatr Child Health* 2006;**42**:423—7.
13. Robson WL, Kabani AM, Leung AK, Fick GH, McKenna AI. The relationship of the serum potassium to the platelet count in children. *Clin Pediatr (Phila)* 1992;**31**:123—5.
14. Manlhiot C, Yeung RS, Clarizia NA, Chahal N, McCrindle BW. Kawasaki disease at the extremes of the age spectrum. *Pediatrics* 2009;**123**:e410—5.
15. Lin MT, Wang JK, Yeh JI, Sun LC, Chen PL, Wu JF, et al. Clinical implication of the C allele of the ITPKC gene SNP rs28493229 in Kawasaki disease: association with disease susceptibility and BCG scar reactivation. *Pediatr Infect Dis J* 2011;**30**:148—52.
16. Anderson MS, Todd JK, Glodé MP. Delayed diagnosis of Kawasaki syndrome: an analysis of the problem. *Pediatrics* 2005; **115**:e428—33.
17. Yeo Y, Kim T, Ha K, Jang G, Lee J, Lee K, et al. Incomplete Kawasaki disease in patients younger than 1 year of age: a possible inherent risk factor. *Eur J Pediatr* 2009;**168**:157—62.
18. Song D, Yeo Y, Ha K, Jang G, Lee J, Lee K, et al. Risk factors for Kawasaki disease-associated coronary abnormalities differ depending on age. *Eur J Pediatr* 2009;**168**:1315—21.