A survey of clinical and laboratory manifestations of Kawasaki disease in children admitted to Children Hospital in Qom, Iran

Mohammad Reza Shokrollahi [1,2], Hosein Heydari [1,2], Leyla Nasehi [3], Zahra Movahedi [1,2]*

[1] Department of Pediatric Infectious Diseases, School of Medicine, Qom University of Medical Sciences and Health Services, Qom, Iran
[2] Pediatrics Infectious Diseases Research Center, Qom University of Medical Sciences and Health Services, Qom, Iran
[3] Department of Radiology, Ronald Reagan Hospital, David Geffen School of Medicine, USA
*Corresponding Author: movahedizahra@yahoo.com

Abstract: Kawasaki disease (KD) is an acute febrile multisystem vasculitis affecting infants. It brings about neurological, pulmonary, renal, and cardiac complications. Currently, it is considered as the major cause of acquired heart diseases in children. Its underlying causes haven't been known yet and there isn't any special laboratory diagnostic test. The main sign and symptoms include fever, bilateral bulbar conjunctivitis, and mucosal redness of the oropharynx, erythema or edema of the peripheral extremities, rash, and unilateral cervical lymphadenopathy. However, with timely treatment and preventive measures, the main complication affecting the heart can be averted. In this study we have investigated the frequency of clinical and laboratory manifestations of KD in children hospitalized in Qom Children Hospital from 2001 to 2011. ***Materials and methods:*** This research is a case series study on 33 children affected by KD hospitalized in Children Hospital in Qom, Iran. All statistical analyses of data obtained were carried out using *SPSS* (Version 11.5). ***Results:*** The frequency of the most important clinical and laboratory test manifestations included fever affecting 33 cases (100%), conjunctivitis 30 (90.9%) , erythema or edema of the peripheral extremes 14 (42.4%), rash 26 (78.8%), cervical lymphadenopathy 20 (60.6%), anemia (decrease of hemoglobin) 18 (54.5%), thrombocytosis 16 (48.50%), and increase of ESR 30 (90.9%). Concerning the risk factor of concomitant heart disorders and the fact that some patients had not received effective treatment, it is incumbent upon general practitioners to exercise more caution about the manifestations of KD, especially incomplete ones.

[Mohammad Reza Shokrollahi, Hosein Heydari, Leyla Nasehi, Zahra Movahedi. **A survey of clinical and laboratory manifestations of Kawasaki disease in children admitted to Children Hospital in Qom, Iran**. *Life Sci J* 2013;10(10s):1-6] (ISSN:1097-8135). http://www.lifesciencesite.com. 1

Key words: Kawasaki Disease (KD); Vasculitis; Children

Introduction

KD is an acute febrile multi-system vacuities affecting children under five years of age with cardiac, renal, pulmonary, neurological complications. At first it described by Dr. Tomisaku Kawasaki in Japan in 1967 (1, 2). The disease occurs worldwide but with a higher prevalence among Asians (1). Approximately 15 to 25% of untreated patients develop coronary artery abnormalities such as aneurysm with the probability of thrombus formation or stenosis of coronary arteries, myocardial infarction, aneurysm rupture and sudden death (1, 3 and 4). Overtaking acute rheumatic fever, it is currently the major cause of acquired heart disease in children in the U.S., Japan, and other developed countries, (1, 5) and is considered as a common rheumatic disease in Iran (6). The origin of disease is unknown. However, the epidemiological aspects of the disease including the age of patients, periodic epidemics with geographic pattern; the self-limited nature of the disease; clinical features of fever, rash, conjunctival hyperemia, and cervical lymphadenopathy are strongly suggestive for an infectious origin (1). KD mainly affects children, with 80% frequency before five years old. (1). This disease is more common in boys than girls with 1.2/1 ratio. In Iran (6) and, regarding other worldwide studies, this ratio has been >1. As to its seasonal prevalence, there has been different cases in special geographical areas. The peak incidence of disease in South Korea, China and Shiraz, Iran was reported in the summer (7), spring and summer, and winter and spring respectively (8).Some clinical features include:

1. Fever: It is generally increasing and unresponsive to antibiotic therapy. Without treatment, it usually lasts for two weeks, but sometimes persisting up to four weeks (1). It is well-known that prolonged fever may be a risk factor of developing coronary artery disease (1, 8, 11, and 10). 2. Bilateral bulbar conjunctivitis, and usually nonexudative; 3. Mucocutaneous changes; 4. Erythema or edema in

extremities; 5. Multiform rashes; 6. Cervical lymphadenopathy: usually unilateral cervical lymphadenopathy ≥ 1.5 cm in size; 7. Perineal skin scaling which can be seen in the acute phase; 8. Irritability; 9. Aseptic meningitis; 10. Diarrhea; 11. Arthritis; 12. Cardiac involvement which is the most important manifestation and can be presented with myocarditis, pericarditis, coronary artery aneurysm or valvular insufficiency (1). Some other manifestations reported include: 1. Sudden blindness (12); 2. Thrombosis and the coronary artery aneurysm (13); 3. Cholangitis (13); 4. Peripheral gangrene (14-13); 5. Hemorrhagic pleural effusion (15); 6. Mediastinal lymphadenopathy (16). The diagnosis is established by fulfillment of the clinical criteria and exclusion of other disease, such as staphylococcal or streptococcal toxin mediated disease; drug reactions; measles, adenovirus, parvovirus B19, or enterovirus infections; rickettsial exanthem; leptospirosis; systemic onset juvenile idiopathic arthritis; and reactive arthritis. is based on typical clinical features. Fever for at least 5 days and at least four of the 5 characteristic criteria include: bilateral bulbar conjunctival injection with limbic sparing and without exudate; erythematous mouth and pharynx, strawberry tongue, and red, cracked lips; a polymorphous, generalized, erythematous rash that can be morbilliform, maculopapular, or scarlatiniform or may resemble erythema multiform; changes in the peripheral extremities consisting of induration of the hands and feet with erythematous palms and soles, often with later periungual desquamation; and acute, nonsuppurative, usually unilateral, cervical lymphadenopathy with at least one node 1.5 cm in diameter.. It must be noted that these symptoms must not be justifiable by any other diseases. Incomplete KD present with fever and fewer than four clinical features. (1, 15, 16, 17, 18). Unfortunately, this group is most susceptible to coronary artery disease (1).

Diagnosis of KD is based on a high index of suspicion and recognition of its clinical features. There is no specific laboratory test for KD (1).

Two-dimensional echocardiography is the best method to determine cardiac problems (1) and a key diagnostic test in patients with inadequate symptoms (6). It should be obtained at the time of diagnosis and repeated at 2 weeks and 6 to 8 weeks after diagnosis (1). Therapy with high-dose IVIG and aspirin initiated within 10 days of the onset of fever substantially decreases progression to coronary artery dilatation and aneurysms, compared with treatment with aspirin alone, and results in more rapid resolution of fever and other clinical and laboratory indicators of acute inflammation. In the acute phase IVIG 2 g/kg within 12 hours, ASA 80 – 100 mg/kg orally 4 times during 24 hours for 14 days should be started, and ASA 3 – 5 mg/kg is taken orally daily for 6 – 8 weeks during convalescence (1). Patients without coronary complications can recover completely without long-term symptoms (1).

Materials and Methods

This case-series study was conducted on 33 patients with KD admitted to children Hospital in Qom, Iran from 2001 to 2011. Data were collected from patients' records using a checklist. The statistical analyses were carried out using *SPSS* (Version 11.5). Results were presented in tables and distributional figures.

Results

Patients age were 5 to 125 months, with a mean of 48.27 months. From a total 33 patients, 22 (66.7%) were boys and 11 (3.33%) were girls, with the boy-girl ratio of 2:1. The patient mostly were admitted in late winter and early spring with 33.3% each, and then autumn and summer, with 24.2% and 9.1% of admissions, respectively. Fever periods ranged from 4 to 15 days, with an average of 8.66 and SD of 2.56 days. In addition, patients' fever fluctuated between 37.5 and 41°C, with an average of 39.12°C and *SD* of 0.8687. Twenty-four of cases (72.7%) had a fever ≥ 39°C. Coronary artery disease was detected in only one patient. The frequency of laboratory and clinical features of patients were measured and shown in Tables 1 and 2. Patients' hemoglobin range was 7.5 to 16.9 g/dl, with a mean of 10.55 and an *SD* of 1.78. Platelet counts were between 1258000/mm^3 and 159,000/mm^3 , with an average of 484218/mm^3 and *SD* of 244371/mm^3. ESR was between 14 to 130 mm/h, with an average of 74.91mm/h and *SD* of 36.61. White blood cells count ranges were 4,500 and 29900/mm^3, with an average of 14081/mm^3. and *SD* of 5777.01. Finally, the neutrophils amount varied between 23 to 90% of total WBC, with an average of 77.16% and *SD* of 12.9. In this study 24 (72.7%) of 33 patients had typical KD while 9 (27.3%) were incomplete. Patients' responses to treatment with IVIG were also analyzed. From 33 patients with KD, 25 (75.8%) have responded to a single dose of IVIG and a high of dose ASA. One person (3%) required a second dose, 6 (18.2%) did not receive IVIG because diagnosis was done after ten days, and in 1 (3%) patient after second doses of IVIG the fever didn't stop and 30mg/kg/day methylprednisolone was administered for 3 days .Out of the 33 patients, 28 (84.9%) recovered completely, and 4 (12.1%) were discharged by personal permission, aborting the treatment process and one of them developed coronary artery ectasia.

Patients were divided into two age groups: A (5 years and younger) and B (older than 5). According to this categorization, 24 (72.7%) fell in Group A, and 9 (27.3%) in Group B. 68.2% of boys and 81.8% of girls were in Group A, and 31.8% of boys and 18.2% of girls in Group B. Most Group A patients were admitted in the hospital in spring and winter while most Group B patients in autumn, winter, and spring. The frequency of clinical features of the two groups did not differ too much. However, irritability, diarrhea, and otitis were most witnessed in Group A whereas arthritis and arthralgia were most apparent in Group B. Comparatively (50% vs. 33.3%), treatment was more successful in Group A than B.

A comparison was drawn between classic and incomplete KD patients. As logically expected, typical features of the disease occurred most in classic patients. Nevertheless, laboratory findings attested to the fact that patients with incomplete form had higher hemoglobin level, platelet count, white blood cells count, neutrophil percentage, ESR, and number of days with fever.

Table 1. Clinical signs of KD in children Hospital, Qom, 2001 – 2011

Clinical symptom	Number	Percentage
Conjunctivitis	30	90.9
Changes in the mucosa of the mouth and throat	30	90.9
Erythema or edema	14	42.4
Rash	26	78.8
Cervical lymphadenopathy	20	60.6
Scaling of perineum	12	36.4
Sca+ling of fingertips	19	57.6
Restlessness	6	18.2
Arthritis	2	6.1
Arthralgia	8	24.2
Diarrhea	1	3
Tachycardia	3	9.1
Pharyngitis	14	42.4
Sinusitis	9	27.3
Cough	13	39.4
Sterile pyuria	3	9.1
Urinary tract infection	0	0
Otitis	7	21.2

Table 2. Laboratory signs of KD in children Hospital, Qom, 2001 – 2011

Laboratory symptom		Percentage	Number
Hemoglobin	Normal	0.439	13
	Increased	3	1
	Decreased	54.5	18
Platelet	Normal	48.5	16
	Increased	48.5	16
White blood cells	Normal	57.6	19
	Increased	33.3	11
	Decreased	6.1	2
Neutrophil	Normal	3	1
	Increased	87.9	29
	Decreased	3	1
Band cell	`1	3	1
	24	3	1
	8	6.1	2
	Negative	81.8	27
ESR	Normal	9.1	3
	Increased	90.9	30
CRP	+1	9.1	3
	+2	6.1	2
	+3	21.2	7
	Negative	24.2	8

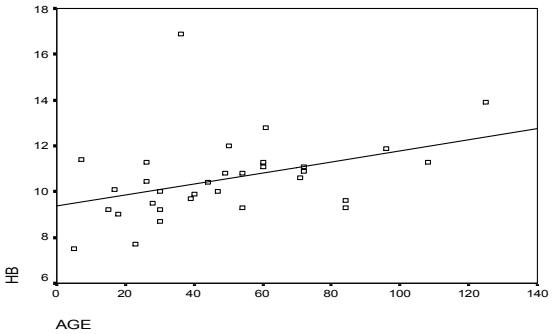

Figure 1: Significant correlation between hemoglobin and age

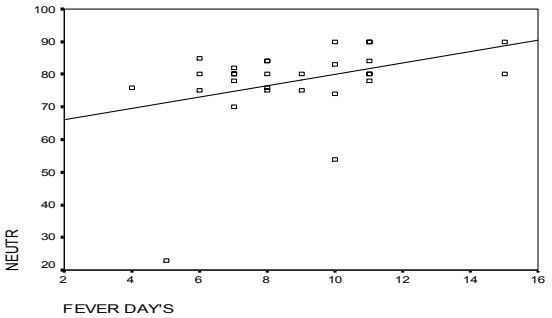

Figure 2: Significant correlation between neutrophil percentage and fever days

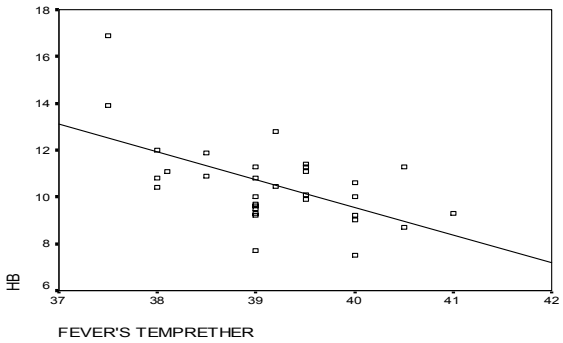

Figure 3: Significant correlation between hemoglobin and fever degree

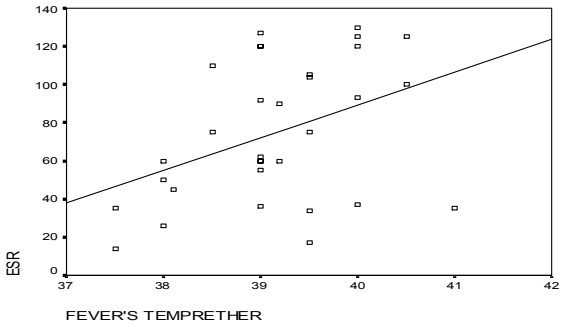

Figure 4: Significant correlation between ESR and fever degree

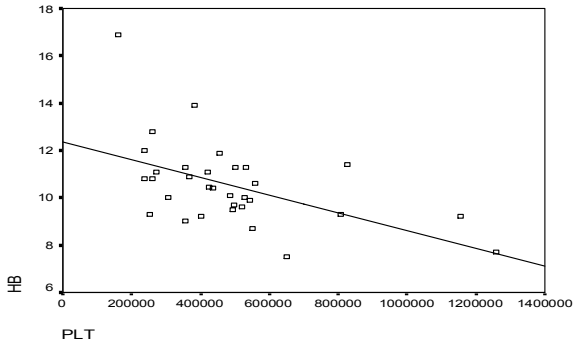

Figure 5: Significant correlation between hemoglobin and platelet

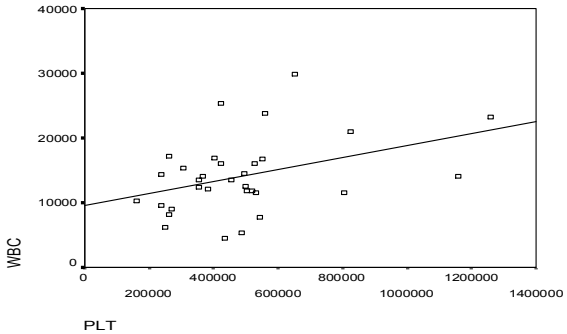

Figure 6: Significant correlation between white blood cells and platelet

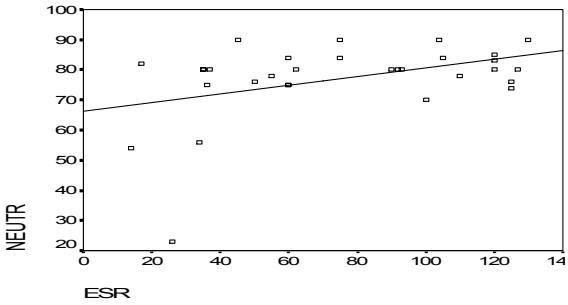

Figure 7: Significant correlation between neutophil percentage and ESR

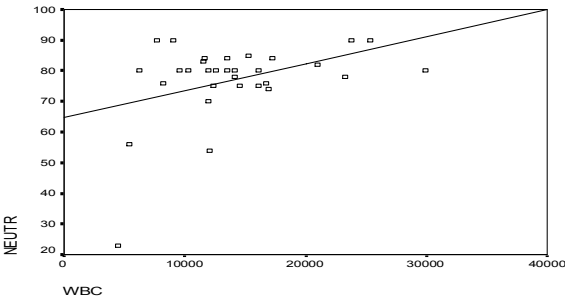

Figure 8: Significant correlation between neutophil percentage and white blood cells

Discussion

KD is an acute febrile multi-system vascuities affecting children with cardiac, renal, pulmonary, and neurological complications. It is most prevalent among Asians (1, 2) and is currently the major cause of acquired heart disease in children (1). Like previous studies, the male-female ratio was > 1 (1, 8,19, and 20). Patients' average days with fever was 8.66 with an SD of 2.56, confirming findings of other studies (17, 19, 21, 20 and 22). Only one patient was diagnosed with coronary artery disease in our study, which is substantially lower than figures by other studies. Similar to other studies in Iran, the peak seasons of admissions were the spring and winter (8). 24 patients (72.7%) were ≤ 5 and 9 (27.3%) were older than 5 as mentioned above (1).Comparing the two Groups of A and B, it was found that the majority of patients were under age 5, supporting findings by research. (1, 19, 6). Group A comprised 75% of classic KD whereas Group B comprised 66.7%. On the other hand, 25 vs. 33.3% of Groups A and B were diagnosed with incomplete KD. Hence, Group A patients were more likely to develop KD, which is in agreement with other studies (23). Children under 5 were also more exposed to restlessness, diarrhea, otitis media, and arthritis, similar to previous studies, and they were also more responsive to treatment (23, 24). In this study, we tried to find a relationship between the variables, so

that they could be used in KD's diagnosis, which is a crucial issue in its treatment.
These include:
1. A direct correlation between age increase and hemoglobin increase, which was found using Pearson correlation coefficient test (p = .05 and r = .397). According the textbooks, low levels of hemoglobin and platelet may aggravates the prognosis of the disease. On the other hand, patients older than 5 are more likely to develop incomplete KD (Figure 1).
2. A direct correlation between increased neutrophil percentage and days of fever using Pearson coefficient test (p = .05 and r = .361) (Figure 2).
3. Indirect correlation between hemoglobin and increasing degrees of fever using Pearson coefficient test (p = .05 and r = .573) (Figure 3).
4. A direct correlation between increasing ESR degrees and increasing degrees of fever using Pearson coefficient test (p=.05 and r = 403) (Figure 4).
5. Indirect correlation between decreasing levels of hemoglobin and increasing levels of platelet using Pearson coefficient test (p = .01 and r = .514). Based on the findings of this research, the more severe KD is, the more reduced hemoglobin and platelet levels are (Figure5).
6. Direct correlation between white blood cells and platelet level using Pearson's correlation test (p = .05 and r = .391). Naturally, the severity of KD raises white blood cells, neutrophil percentage, ESR count, and platelet count in parallel. Therefore, a direct correlation between these laboratory parameters in Numbers 6, 7, and 8 was expected (Figure6).
7. A direct correlation between neutrophils percentage and increasing levels of ESR using Pearson correlation test(p = .05 and r = .411) (Figure 7).
8. A direct correlation between increasing levels of neutrophil and increasing white blood cell count using Pearson correlation test (p = .05 and r = .4) (Figure 8).

And finally: Regarding the comparison of age groups, it was found that much fewer girls than boys in Group B developed KD. 68.2% boys from Group A and 31.8% from Group B; 81.8% girls from Group A and 18.2% from Group B). If confirmed in larger samples, it is proposed that the higher male susceptibility to KD be explored in future research.

Group A patients admitted in the hospital mostly during spring and winter whereas children from Group B were admitted mainly during summer and autumn. Considering the fact that most children older than 5 go to daycare centers or school, it is recommended that this issue also be taken into account in prevention strategies. Concerning the significant correlation between hemoglobin reduction and platelet rising, it is proposed that some research be carried out at the cellular-molecular level to discover the mechanism of this phenomenon. Consequently, causes of anemia and thrombocytosis can be followed, leading support to the origins of KD.

Conclusion

KD involves cardiac disorders, which may turn into long-term diseases or increase mortality. There were 18.2% of patients who had not received proper treatment, which indicates that our general practitioners must be more cautious in dealing with symptoms of KD, particularly the incomplete ones.

References

1) Robert M, Kliegman MD; Richard E; Behman, MD; Bal B; Jenson, MD; Jan S. Abramson, MD; etal. Nelson textbook of pediatrics, 19th ed, 2011;862-867.
2) Elizabeth KE, Ahamed MZ, Praveen KS. Atypical Relapsing Course of Kawasaki Disease with Hemorrhagic Serous Effusions and Hepatic Dysfunction. Indian Pediatr. 2007 Oct 7;44(10):785-787.
3) Newburger JW, Fulton DR. Kawasaki disease. Curr Opin Pediatr. 2004 Oct; 16(5): 508-14.
4) 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, Endocarditic and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004 Oct 26; 110(17): 2747-71.
5) Soncagi A, Devrim I, Karagoz T, Dilber E, Celiker A, Ozen S, et al. Septated pericarditis associated with Kawasaki disease: a brief case report. Turk j pediatr. 2007; 49: 312-314.
6) Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev. 2003;(4).
7) Mohammad Hasan Moradinejad, Abdolrazagh Kiani. Kawasaki Disease in 159 Iranian Children. Iran J Ped. Sep 2007; 17(3):241-246.
8) Freeman AF, Shulman ST. Kawasaki disease: summery of the American Heart Association guidenlines. Am Fam Physician.2006 Oct 1; 74(7):1149-50.
9) Lee KY, Han JW, Lee HS, Hong GH, Hahn SH, Lee JS, et al. Epidemiologic study of Kawasaki disease at a single hospital Daejeon, Korea (1987 through 2000). Pediatr Infect Dis J. 2004

Jan; 23(1): 52-5.
10) Sadeghi E, Amin R, Ajamee GH. Kawasaki syndrome: the Iranian experience. East Mediterr Health J. 2001 Jan-Mar; 7(1-2): 16-25.
11) Baer AZ, Rubin LG, Shapiro CA, Sood SK, Rajan S, Shapir Y, et al. Prevalance of coronary artery lesions on the initial echocardiogram in Kawasaki syndrome. Arch Pediatr Adolesc Med. 2006 Jul; 160(7):-686-90.
12) Farvardin M, Kashef S, Aleyasin S, Nabavizadeh SH, Sajjadi M, Safari M. Sudden unilateral blindness in a girl with Kawasaki disease. J Pediatr Ophthalmol Strabismus. 2007 Sep-Oct; 44(5): 303-4.
13) Brenner JL, Jadavji T, Pinto A, Traverenen C, Patton D. Severe Kawasaki disease in infants: two fatal cases. Can J Cardiol 2000 Oct; 16(10):1206.
14) Bonte I, Mahr A, Laroach L, Guillevin L, Robineau M. Peripheral gangrene in adult-onset Kawasaki disease. Scand J Rheumatol. 2005; 34(1): 71-3.
15) D'Souza S, Khbchandani RP, Shetty AK. Kawasaki disease presenting with hemorrhagic pleural effusion. J Trop Pediatr.2006 Aug; 52(4):299-301.
16) Bosch Marcet J, Serres Creixams X, Penas Boira M, Inaraja Martinez L. Mediastinal lymphadenopathy: a variant of incomplete Kawasaki disease.Acta Paediatr. 1998 Nov; 87(11):1200-2.
17) Zhong-Dong Du, Di Zhao, MD; Junbao Du, Yong- Lan Zhang MD, Yao Lin, Chong Liu, et al. Epidemiologic Study on Kawasaki Disease in Beijing from 2000 Through 2004. The Pediatric Infection Disease Journal. May 2007; 26(5):449--451.
18) Pickering L.K, Baker C.J, Kimberlin D.W, Long S.S. Red Book. 2012 Report of the committee on infectious disease.29th Edition.454-459
19) Anderson MS, Todd JK, GLODE MP. Delayed diagnosis of Kawasaki syndrome: an analysis of the problem. Pediatrics. 2005 Apr; 115(4): e428-33.
20) Saffar MJ, Reshidighader F. Kawasaki disease in East Mazandaran, Islamic Republic of Iran, 1997-2002. East Mediterr Health J. 2005 Jan-Mar;11(1-2):28-35.
21) Zhang W, Li Q, Zhao XD, Tang XM, Wang XG, Wang M, et al. Clinical analysis of 942 cases of Kawasaki disease. Zhonghua Er Ke Za Zhi.2006 May; 44(5): 324-8.
22) Hsieh YC, Wu MH, Wang JK, Lee PI, Lee CY, Huang LM. Clinical features of atypical Kawasaki disease. J Microbiol Immunol Infect. 2002 Mar; 35(1):57-60.
23) Lee KY, Hong JH, Han JW, Lee JS, Lee BC, Burgner D. Features of the Kawasaki disease at the extremes of age. J Paediatr Child Health. 2006 Jul-Aug; 42(7-8):423-7.
24) Sittiwangkul R,Pongprot Y, Thongsongkrit W, Silvilairat S, Phornphutkul C. Kawasaki disease in Thai infants compared with older children. Ann Trop Paediatr.2004 Mar; 24(1):59-63.

7/16/2013