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Clinical Manifestations of Kawasaki Disease: What Are the Significant Parameters?

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SUMMARY The initial differential diagnosis of Kawasaki disease (KD) from other acute febrile illnesses infants and children is particularly difficult in patients who exhibit incomplete criteria. The objective of this study was to determine the differences in the clinical and laboratory findings between KD patients and those who were initially suspected of having KD but eventually had other diagnoses. One hundred and fourteen pediatric patients who were initially diagnosed with suspected KD were included. Eighteen cases were finally diagnosed with another disease. The only demographic data that were significantly different between the groups were body height and the duration of fever. The KD group exhibited more classical clinical criteria than those who were finally diagnosed with another disease. The erythrocyte sedimentation rate (ESR) and platelet count were significantly higher in the KD group than in the non-KD group. An ESR $\geq$ 40 mm/hour had a diagnostic sensitivity of 90.5%, a specificity of 66.6%, a positive predictive value of 93.4%, and a negative predictive value of 57.1%. The incidence of coronary aneurysm in this study was 6.2%. There was no correlation between ESR and coronary aneurysm. We conclude that the clinical criteria are the basis for the diagnosis of Kawasaki disease but the ESR can be helpful in pediatric patients with acute febrile illness who do not exhibit all clinical criteria.

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology, frequently affecting small to mid-size arteries, especially the coronary arteries. This disease predominantly affects infants and young children. Coronary artery aneurysms develop in 15-25% of children who do not receive treatment. Treatment with intravenous immunoglubulin G (IVIG) dramatically reduces the incidence to 5-10%.[1,2] Approximately 4% of all patients may progress to ischemic heart disease.[3] Data from the Thai National Registry in 2002-2003 showed that 22.2% of the patients who were diagnosed with Kawasaki disease had $\leq$ 3 classic criteria.[4] Thus, the differentiation between Kawasaki disease and non-Kawasaki disease relying solely on clinical signs and symptoms is difficult.

Previous studies showed evidence of coronary artery aneurysms in both typical Kawasaki disease and incomplete Kawasaki disease.[5-9] Coronary artery aneurysms occurred significantly more often in patients with a delayed diagnosis of Kawasaki disease,[10,11] especially when the total duration of fever

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was longer than 8 days.[11] The American Heart Association recommended a new algorithm to aid clinicians to decide which children with fever for more than five days and less than the four classic criteria of Kawasaki disease, but who were still suspected of having Kawasaki disease, should undergo early IVIG treatment and treatment with anti-inflammatory agents. The objective of this guideline is to emphasize an early start of the treatment with IVIG to prevent coronary artery aneurysm. Following this guideline, general physicians and pediatricians frequently over-diagnosed Kawasaki disease which led to an overuse of IVIG.

Due to the implications of Kawasaki disease, many pediatricians and general practitioners are aware of its prevalence in acutely febrile infants and children. As 22.2% of our Kawasaki patients have ≤ 3 classic criteria, the differentiation between Kawasaki disease and fever from other causes is difficult. The objective of this study was to determine the differences in clinical symptoms, signs, and laboratory findings between Kawasaki patients and those who were initially suspected of having Kawasaki disease but who were eventually given other diagnoses, in order to improve the early recognition of Kawasaki disease and provide a better differential diagnosis for patients with Kawasaki-like symptoms.

MATERIALS AND METHODS

Patients

A retrospective study was conducted for all pediatric patients who were initially diagnosed with Kawasaki disease (acute phase) upon admission and were admitted at the Pediatric Department, Siriraj Hospital, from January 1st, 2001 and December 31st, 2006. This study was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University.

Clinical symptoms and signs were studied. The classic criteria for the diagnosis of Kawasaki disease consist of high fever accompanied by the presence of at least four of the five following manifestations: i) bilateral conjunctival injection, ii) changes in the lips and oral cavity, iii) non-purulent cervical lymphadenopathy, iv) polymorphous exanthema, and v) changes in the extremities.[12] Patients who have less than four of these criteria can be diagnosed with KD when coronary artery disease is detected by echocardiography.

Following the American Heart Association recommendations, laboratory tests such as erythrocyte sedimentary rate (ESR), C-reactive protein (CRP), serum albumin, platelet count, WBC, hematocrit, hemoglobin, alanine aminotransferase (ALT), and urinalysis were assessed.

Patients in the non-KD group were finally confirmed with another diagnosis if i) the fever resolved without the typical peeling, and ii) the fever resolved with less than three supplementary laboratory criteria (anemia for age, WBC ≥ 15,000 cells/mm^3, platelet count ≥ 450,000 cells/mm^3, hypoalbuminemia, elevated liver enzyme, and sterile pyuria) and a normal echocardiography.

Echocardiography

Echocardiography was performed initially to assist the diagnosis of Kawasaki disease. If any complication was detected, echocardiography was repeated at week 2, and week 6 or week 8 of the disease. An echocardiogram was considered positive if any of the following three conditions were met: a Z score of the LAD or RCA ≥ 2.5, the coronary arteries met the Japanese Ministry of Health criteria for aneurysms, or ≥ 3 other suggestive features existed, including perivascular brightness, lack of tapering, decreased LV function, mitral regurgitation, pericardial effusion, or Z scores of the LAD or RCA of 2–2.5.[12]

Statistical analysis

Data were analyzed with SPSS for Windows (Version 14). Continuous data (age, gender, weight, height, duration of fever, clinical criteria, number of cases with coronary aneurysm or abnormal coronary artery, WBC count, hemoglobin level, platelet count, and serum albumin level) were expressed as frequency or mean ± the standard deviation (SD) or median with range. Comparisons between groups were analyzed with the unpaired *t*-test or Mann-Whitney U-test when appropriate. The chi-square was used to assess the association between the risk factors and the outcome variables.

RESULTS

During the study period, 114 pediatric patients were initially diagnosed with Kawasaki disease. The mean age was 32.8 ± 28.3 months. Sixty-eight (57.6%) cases were male. The duration of fever was 1-21 days. Eighteen cases were finally diagnosed with other diseases as shown in Table 1. The demographic data of both groups of patients, the KD and the non-KD group, are shown in Table 2. No significant difference was seen regarding height and duration of fever between the groups.

In the KD group, only 69 cases (71.9%) had ≥ 4 clinical criteria (complete Kawasaki disease) and the remainder (28.1%) had < 4 clinical criteria. They were diagnosed as incomplete Kawasaki disease. In the non-KD group, only 1 patient had 4 clinical criteria and he was finally diagnosed with infectious mononucleosis which was confirmed by serology. The differences in the clinical symptoms and signs are presented in Table 3. All classical clinical criteria were more common in the KD group than in the non-KD group. But there was no statistically significant difference in the clinical criteria between the incomplete KD and the non-KD group as shown in Table 4.

The average values of hemoglobin, hematocrit, platelet count, and ESR were significantly different between the groups as shown in Table 5. In contrast, WBC count and serum albumin showed no statistical difference between the groups. CRP was not analyzed because it was only recently reported as a quantitative measurement. Neither ALT data nor urinalysis were recorded in all patients.

As shown in Table 5, the ESR and platelet counts in the KD group were significantly higher than in the non-KD group. The analysis of ESR with an estimation of the Receiver Operating Characteristic (ROC) curve showed that an ESR ≥ 40 mm/hour increased the likelihood of Kawasaki disease 2.72 times compared to the non-KD patients, with a sensitivity of 90.5%, a specificity of 66.6%, a positive predictive value of 93.4%, and a negative predictive value of 57.1%, respectively. The predicted probability of Kawasaki disease in relation to the ESR is presented in Fig. 1.

Abnormal coronary arteries were found in 28 (28.9%) patients with KD by echocardiography; 22 cases had coronary ectasia and 6.2% had a coronary

Table 1 Diagnoses of all patients

Patient group	Number
KD	96
Non-KD	18
Viral infection, unspecified	7
Infectious mononucleosis	1
Dengue hemorrhagic fever	1
Dengue shock syndrome	1
Urinary tract infection	1
Angioneurotic edema	1
Scarlet fever	1
Arthritis	1
Systemic vasculitis	1
Measles	1
Occult bacteremia	1
Fever, unspecified	1

Table 2 Demographic data of the patients

	KD (n = 96)	**Non-KD** (n = 18)	***p*-value**
Age (months)	30.1 ± 24.1	47.2 ± 42.7	0.115
Male, n (%)	58 (60.4%)	10 (55.6%)	0.700
Height (cm)	89.1 ± 19.1	101.1 ± 24.7	0.030*
Weight (kg)	13.0 ± 5.7	16.7 ± 11.6	0.213
Duration of fever (days)	7.0 ± 3.5	5.0 ± 3.1	0.024*

*Signifies statistical significance

aneurysm. We also found that there was no correlation between the ESR and coronary aneurysms because most of the patients who had a coronary aneurysm had an ESR between 52-88 mm/hour, whereas many patients who had a higher ESR did not have a coronary aneurysm ($p = 0.42$).

As for the platelet count, the ROC curve showed that a platelet count of ≥ 450,000 cells/mm^3 increased the likelihood of Kawasaki disease by 1.7 times compared to the non-KD patients with a sensitivity of 46.3%, a specificity of 72.2%, a positive predictive value of 89.8%, and negative predictive value of 20.3%, respectively.

DISCUSSION

The median age of the Kawasaki patients in

Table 3 Clinical symptoms and signs: differences between the KD and non-KD groups

Clinical criteria	**KD** (n = 96)	**Non-KD** (n = 18)	***p*-value**
Mucositis	92 (95.8%)	7 (38.9%)	< 0.001*
Rash	82 (85.4%)	11 (61.1%)	0.015*
Eye	77 (80.2%)	6 (33.3%)	< 0.001*
Edema	62 (64.6%)	5 (27.9%)	0.004*
Lymphadenopathy	40 (41.7%)	3 (16.7%)	0.009*

* Signifies statistical significance

Table 4 Clinical symptoms and signs: differences between the incomplete KD (iKD) and non-KD groups

Clinical criteria	**iKD** (n = 26)	**Non-KD** (n = 18)	***p*-value**
Mucositis	23 (88.5%)	7 (38.9%)	0.001*
Rash	15 (57.6%)	11 (61.1%)	0.712
Eye	12 (46.2%)	6 (33.3%)	0.456
Edema	8 (30.8%)	5 (27.8%)	0.893
Lymphadenopathy	7 (26.9%)	3 (16.7%)	0.464

* Signifies statistical significance

Table 5 Laboratory values of the patients

Investigation	**KD** (n = 96)	**Non-KD** (n = 18)	***p*-value**
Hemoglobin (g/dl)	10.5 ± 1.1	11.3 ± 1.1	0.007*
Hematocrit (%)	31.9 ± 3.2	34.6 ± 3.5	0.001*
WBC (cells/mm^3)	15,704 ± 6,534	12,817 ± 8,548	0.106
Neutrophils (%)	59.9 ± 15.4	54.6 ± 27.0	0.439
Lymphocytes (%)	30.2 ± 13.9	30.7 ± 22.0	0.927
Platelets (cells/mm^3)	433,115 ± 164,327	317,372 ± 142,320	0.006*
ESR (mm/hour)	73.7 ± 27.1	34.2 ± 23.9	< 0.001*
Albumin (g/dl)	3.4 ± 0.5	3.6 ± 0.6	0.281

*Signifies statistical significance

our study 30.1 ± 24.1 months, which was similar to a previous publication.[4] Males were more dominant than females. The mean duration of fever in our Kawasaki patients was 7.0 ± 3.5 days, which was longer than for non-Kawasaki patients (5.0 ± 3.1 days, $p = 0.024$). This can be explained by that at the onset of Kawasaki disease not all the typical features were immediately evident, some patients were therefore not diagnosed with KD and the fever not treated appropriately until Kawasaki disease was considered in those patients.

The incidence of coronary aneurysm in this study was 6.2% which was similar to that of the general population.[12] The Kawasaki patients exhibited more classical clinical criteria than the non-Kawasaki patients. Twenty-seven cases (28.1%) of Kawasaki patients had < 4 clinical criteria, which was similar to a previous study,[4] and were diagnosed as incomplete KD (iKD). When we compared the clinical criteria between the iKD and non-KD group, the result indicated that we could not use clinical criteria alone to differentiate between these two groups. Supplementary laboratory investigations can be beneficial in this situation. One of the non-Kawasaki patients, however, had all the criteria of typical Kawasaki disease; thus the diagnosis of Kawasaki disease should be based on the exclusion of other diseases.

Referring again to the AHA guideline,[12] six supplementary laboratory investigations were used to guide the physician to the possibility of Kawasaki disease. In this study, some laboratory tests were obtained for all patients and significant differences could be demonstrated in hemoglobin, hematocrit, ESR, and platelet count. Hemoglobin and hematocrit were not, however, differentiated because these are age-related numbers (10.5 g/dl *vs.* 11.3 g/dl, and 31.9% *vs.* 34.6%, respectively). We did not find a clear cutoff point for the platelet count as a predictor of Kawasaki disease, as the ROC curve showed a sensitivity of only 46.3%. This can be explained by that thrombocytosis often occurs after the first week of the disease. It is difficult therefore, to differentiate Kawasaki patients from non-Kawasaki patients during the early stage (before 7 days of fever) by the platelet count only. It was also surprising to us that there was no difference in the WBC between both groups.

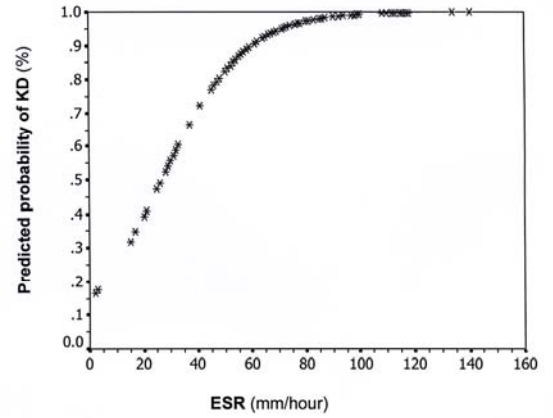

Fig. 1 Relationship between ESR and Kawasaki disease.

The ESR value of ≥ 40 mm/hour was selected for differentiating KD patients from the non KD group following the AHA/ACC recommendations.[12,15] To the best of our knowledge this is the first study in Thai children to validate that an ESR ≥ 40 mm/hour showed a significant statistical difference between both groups. The value from the ROC curve showed a sensitivity of 90.5%, a specificity of 66.6%, and a positive predictive value of 93.4%. The predicted probability of Kawasaki disease thus increased with a higher ESR.

Kawasaki disease remains the most important cause of acquired coronary artery disease in children. Physicians must remain aware of the possibility of this disease in acute febrile illness in infants and in children with other clinical manifestations which cannot be explained by other causes. Clinical criteria are, of course, used to make the diagnosis but some typical clinical criteria have a late onset and can therefore delay the diagnosis: this may lead to coronary artery aneurysm. However, a hasty diagnosis of Kawasaki disease may cause unnecessary use of IVIG and delay the diagnosis of other diseases. This study led us to conclude that the ESR is a useful tool when the suspicion of Kawasaki disease exists in acutely febrile Thai infants and children with an ESR ≥ 40 mm/hour.

This retrospective study had limitations deriving from the data collection. Some laboratory results were not recorded, such as ALT, and some were recorded by a different method, such as CRP

which was previously reported as a qualitative value (1+ to 4+) and is currently reported as a quantitative value. But in general practice, all supplementary laboratory tests including serum electrolytes, must be obtained because they can be useful for the prediction of coronary aneurysm and of IVIG unresponsiveness.[13,14]

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