ORIGINAL ARTICLE

The Clinical Manifestations and Risk Factors of a Delayed Diagnosis of Kawasaki Disease

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Background: Kawasaki disease (KD) is an acute febrile vasculitis and may cause coronary artery abnormalities. Due to the higher incidence in Asian countries, most pediatricians in Taiwan are familiar with KD. However, there are still some patients being diagnosed 10 days after the onset of the illness and not receiving a highly effective therapy. In this study, we analyzed the risk factors and clinical manifestations of patients with a delayed diagnosis of KD.

Methods: A retrospective review was made of the medical records of the patients diagnosed with KD at our institution between January 1996 and December 2005. The patients were divided into 2 groups: early-diagnosis group (EDG: diagnosis was made within 10 days after the onset of the fever) and delayed-diagnosis group (DDG: diagnosis was made 10 days after the onset of the fever).

Results: Fourteen of a total of 78 children (17.9%) were grouped into the DDG group, and 64 into the EDG group. There were no statistical differences between the 2 groups in terms of age, gender, number of antibiotics used, day of the first medical visit, total days of skin rash, conjunctivitis, mucosa changes, lymphadenopathy or laboratory examinations except for the higher white blood cell count and serum immunoglobulin G level in the DDG group. The patients in the EDG group had a clustered onset of symptoms as compared to the DDG group with a dispersed and late onset of symptoms. There was a higher risk of coronary artery abnormalities in the DDG group than the EDG group (42.9% *vs.* 14.1%; $p = 0.036$), and in the patients with KD who were younger than 1 year (29.0% *vs.* 12.7%; $p = 0.043$).

Conclusion: Patients with delayed diagnosis of KD were associated with higher risk of developing coronary arterial lesions. It is necessary to develop a diagnostic test for KD and provide more education to health care providers for early recognition of KD. [*J Chin Med Assoc* 2007;70(9):374–379]

Key Words: coronary artery abnormalities, delayed diagnosis, Kawasaki disease

Introduction

Kawasaki disease (KD) is an acute febrile vasculitis and the most common acquired heart disease in children worldwide, and is associated with a higher incidence in Asian countries. Dr Tomisaku Kawasaki originally described KD in a Japanese-language medical journal in 1967.[1] A prompt diagnosis is critically important, because the major complications (coronary artery abnormalities) can be reduced from 20–25% to 3–5% by the administration of intravenous immunoglobulin (IVIG) within 10 days of the onset of illness.[2] In addition, KD was recently reported as a potential risk factor for adult ischemic heart disease and sudden death in early adulthood.[3]

A previous study revealed that 30% of the patients hospitalized for treatment of KD were diagnosed after day 10 of the illness.[4] In spite of the relatively high occurrence of delayed diagnosis of KD, information on the possible risk factors and clinical manifestations is still limited. Identifying the specific characteristics of a delayed diagnosis of KD might be helpful for avoiding a delayed diagnosis, promoting an earlier recognition of KD and reducing the rate of coronary artery complications. The purpose of this study was to investigate the risk factors and clinical manifestations in children with

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a delayed diagnosis of KD. We hypothesized that the patients with a delayed diagnosis of KD might have a younger age, more delayed first physician visit, receive more antibiotics for other diagnoses, or an atypical clinical presentation.

Methods

The medical records of the patients diagnosed with KD between January 1996 and December 2005 in our institution were retrospectively reviewed. All charts were identified by the discharge diagnosis (*International Classification of Disease, Ninth Revision* [ICD-9] code 446.1) and reviewed by 2 investigators to ensure that patients met the clinical criteria for KD. Any medical charts with incomplete records were excluded. We collected detailed information from the medical records including demographic characteristics, echocardiographic results, drugs prescribed, laboratory data, clinical symptoms (day of onset and duration), and number of days from the onset of symptoms to diagnosis. Coronary artery abnormalities were documented as present if they were seen on any echocardiogram on either the day of presentation or during follow-up.

Definitions

The diagnostic criteria of KD by the American Heart Association was established by an existence of a high fever for more than 5 days and 4 or 5 of the following 5 criteria: (1) bilateral bulbar conjunctival infection, generally nonpurulent; (2) changes in the mucosa of the oropharynx, including an infected pharynx, infected and/or dry fissured lips and a strawberry tongue; (3) changes in the peripheral extremities, such as edema and/or erythema of the hands or feet in the acute phase, or periungual desquamation in the subacute phase; (4) rash, primarily truncal, polymorphous but nonvesicular; and (5) cervical lymphadenopathy, ≥ 1.5 cm, usually in the unilateral cervical region.[5]

The number of days of specific signs was defined as the interval in days from the onset of signs to the resolution of signs. Patients with an early diagnosis were defined as those having diagnosis of KD made within or by 10 days after the onset of the fever. Patients with a delayed diagnosis were defined as having diagnosis of KD made more than 10 days after the onset of the fever. The criteria of the coronary artery abnormalities detected by echocardiography included: (1) a diameter of the internal lumen of more than 3 mm; (2) an internal diameter of a segment 1.5 times greater than that of an adjacent segment (saccular or fusiform aneurysm); and (3) irregular surface and/or perivascular brightness of the coronary arterial wall.[6]

Statistical analysis

Pearson's χ^2 test and Student's t test were used for statistical analyses and comparisons between the 2 groups. The collected data that were not normally distributed were compared by using the Mann–Whitney rank sum test. Pearson correlation coefficients were calculated to establish any correlations between the demographic data, clinical manifestations and laboratory findings in the patients. Statistical significance was defined as a p value < 0.05.

Results

Patient characteristics

During a 10-year period, 78 patients with detailed medical records and diagnosed with KD (ICD-9 code 446.1) were enrolled in this study. Fifty-seven patients with unsure recall of clinical history, incomplete medical records or laboratory data were excluded from the study. Sixty-four (82.1%) of the 78 patients were categorized into the early-diagnosis group (EDG, Group I) (mean age, 25 ± 24 months; male/female ratio, 40/24), and 14 (17.9%) children were categorized into the delayed-diagnosis group (DDG, Group II) (mean age, 23 ± 19 months; male/female ratio, 9/5). There were no significant differences in the patient characteristics, including age and gender, between the 2 groups.

Clinical characteristics and laboratory features

The duration of symptoms and first contact with a medical provider are shown in Table 1. There was a trend for the total number of days of a fever, skin rash, mucosa changes and extremity changes to be longer in Group II patients than in Group I patients, but only the difference in duration of fever was statistically significant. Between the 2 groups, the number of antibiotics prescribed and day of the first medical contact were similar, and there were no significant differences between the 2 groups.

With regard to laboratory findings, the white blood cell count (WBC) on admission was significantly higher in DDG patients than in EGD patients (23.5×10^3 *vs.* $14.9 \times 10^3/\mu L$; $p = 0.043$) (Table 2). The levels of immunoglobulin G were also significantly higher in Group II patients (766 ± 431 *vs.* $1{,}377 \pm 711$ mg/dL; $p = 0.001$).

Table 1. The potential risk of a delayed diagnosis in patients with Kawasaki disease*

Variables	Group I ($n=64$)	Group II ($n=14$)	p
Days of fever	7.1±1.6 (6.7–7.5)	14.0±3.2 (12.1–15.9)	<0.010†
Days of skin rash	4.4±1.6 (4.0–4.8)	6.5±5.2 (3.4–9.7)	0.334
Days of conjunctivitis	6.2±1.5 (3.8–4.6)	6.0±4.3 (3.4–8.6)	0.269
Days of mucosa changes	4.3±1.5 (3.9–4.7)	5.8±3.3 (3.6–7.9)	0.221
Days of extremity changes	2.7±1.7 (2.2–3.2)	4.7±3.2 (2.2–7.1)	0.072
Presence of lymphadenopathy	46.9%	57.1%	0.688
Number of antibiotic prescriptions	1.6±0.7 (1.4–1.9)	1.6±0.5 (1.1–2.1)	0.960
First contact with a medical provider, day of illness	2.6±1.4 (2.3–3.0)	2.6±1.0 (2.0–3.2)	0.934

**Data are presented as mean±standard deviation (95% confidence interval) or %; †statistically significant at $p<0.05$. Group I = early-diagnosis group; Group II = delayed-diagnosis group.*

Table 2. Laboratory findings of patients with an early/delayed diagnosis of Kawasaki disease*

Characteristic	Group I ($n=64$)	Group II ($n=14$)	p
WBC (×1000/μL)	14.9±4.8 (13.7–16.1)	23.5±19.8 (12.0–35.0)	0.043†
Platelets (×1000/μL)	357±163 (317–398)	407±205 (288–525)	0.325
CRP (mg/dL)	11.0±6.8 (9.4–12.8)	9.3±8.7 (4.2–14.3)	0.424
IgG (mg/dL)	766±431 (645–887)	1,377±711 (947–1,806)	0.001†
IgA (mg/dL)	83±53 (68–98)	109±66 (69–149)	0.114
IgM (mg/dL)	130±48 (116–143)	169±86 (117–222)	0.166
Albumin (g/dL)	3.8±0.5 (3.7–4.0)	3.6±0.4 (3.2–4.0)	0.231
HDL (mg/dL)	24±10 (21–27)	25±10 (18–32)	0.736
LDL (mg/dL)	77±25 (70–84)	83±31 (61–105)	1.000
Triglyceride (mg/dL)	142±75 (120–163)	126±44 (95–158)	0.675
Cholesterol (mg/dL)	129±30 (121–137)	135±30 (113–157)	0.589
AST (U/L)	52±41 (41–62)	106±196 (13–225)	0.774
ALT (U/L)	74±84 (53–95)	112±173 (7–216)	0.317

**Data are presented as mean±standard deviation (95% confidence interval); †statistically significant at $p<0.05$. Group I = early-diagnosis group; Group II = delayed-diagnosis group; WBC = white blood cell count; CRP = C-reactive protein; IgG/A/M = immunoglobulin G/A/M; HDL = high-density lipoprotein; LDL = low-density lipoprotein; AST = aspartate aminotransferase; ALT = alanine aminotransferase.*

Physician visit and the initial diagnosis

The majority of the patients in each group (EDG, 73%; DDG, 92%) had sought their first medical attention during the first 3 days of their illness. Overall, 76.9% of the patients with KD first presented to a physician between days 1 and 3 of their illness. No significant difference between these 2 groups for the mean day of their first physician visit was noted. At the first visit, many different diagnoses were given and only 14 of 78 patients (17.9%) had a diagnosis of KD initially. The initial diagnoses of all the patients are listed in Table 3. An upper respiratory tract infection, acute pharyngitis and lymphadenitis were the 3 most common initial diagnoses in both groups.

The onset of the physical signs of KD

A trend of developing signs of KD tightly clustered within 5 days of the illness was demonstrated in the EDG group. In contrast, DDG group patients had the

Table 3. Diagnoses of the patients with Kawasaki disease at the first medical visit*

Diagnosis	Group I	Group II
Upper respiratory infection	17 (26.6)	9 (64.3)
Kawasaki disease	14 (21.9)	
Acute pharyngitis	7 (10.9)	2 (14.3)
Lymphadenitis	7 (10.9)	2 (14.3)
Urinary tract infection	4 (6.3)	
Scarlet fever	3 (4.7)	
Acute gastroenteritis	3 (4.7)	
Acute tonsillitis	2 (3.1)	1 (7.1)
Acute otitis media	2 (3.1)	
Bronchopneumonia	2 (3.1)	
Acute bronchiolitis	1 (1.6)	
Enterovirus infection	1 (1.6)	
Roseola infantum	1 (1.6)	
Total	64 (100.0)	14 (100.0)

**Data are presented as n (%). Group I = early-diagnosis group; Group II = delayed-diagnosis group.*

Table 4. Onset of the symptoms and signs of Kawasaki disease*

	Group I ($n=64$)	Group II ($n=14$)	p
Mucosa changes on the day of illness	3.8±1.5 (3.4–4.2)	8.2±3.7 (5.8–10.6)	<0.001†
Conjunctivitis on the day of illness	3.9±1.3 (3.6–4.3)	7.6±3.6 (5.4–9.8)	<0.001†
Skin rash on the day of illness	3.5±1.6 (3.1–3.9)	6.2±3.9 (3.7–8.5)	0.026†
Lymphadenopathy on the day of illness	3.1±1.7 (2.4–3.7)	6.1±3.7 (2.9–9.2)	0.032†
Extremity changes on the day of illness	4.9±1.4 (4.5–5.3)	9.5±3.9 (6.5–12.5)	<0.001†

*Data are presented as mean±standard deviation (95% confidence interval); †statistically significant at $p<0.05$.

Table 5. Coronary artery abnormalities in patients with Kawasaki disease according to age*

Age (mo)	Group I ($n=64$)	Group II ($n=14$)	Total
<12 ($n=31$)	5/64 (7.8)	4/14 (28.6)	9/31 (29.0)
≥12 ($n=47$)	4/64 (6.2)	2/14 (14.3)	6/47 (12.7)
Total	9/64 (14.1)	6/14 (42.9)	$p=0.043$†
			$p=0.036$†

*Data are presented as n (%); †statistically significant at $p<0.05$.

onset of the signs dispersed over 10 days. The onset of additional signs in both groups is compared in Table 4. There was no statistical difference in the first medical contact between the 2 groups (2.6±0.7 *vs.* 2.6±1.0 days; $p=0.934$).

Coronary artery abnormalities

In this study, a total of 15 patients with KD (19.2%) had coronary artery abnormalities recognized by echocardiography at either the initial presentation or during follow-up despite any IVIG therapy (Table 5). Group II patients had a statistically significant higher incidence of coronary artery abnormalities (42.9% *vs.* 14.1%; $p=0.036$). On the other hand, higher incidence of coronary artery abnormalities in patients whose age was less than 1 year was found (29.0% *vs.* 12.7%; $p=0.043$).

Discussion

The incidence of KD varies among different countries, and Asian countries allegedly have a higher incidence than Western countries. In Taiwan, the annual KD incidence is reported to be around 66/100,000 in children <5 years old, and it is the second highest in the world.[7] Therefore, KD is familiar to most pediatricians in Taiwan. Therefore, it should be an early consideration as a differential diagnosis in febrile children in order to decrease the rate of delayed diagnosis. A previous study demonstrated that 30% of KD patients were diagnosed after 10 days of the illness.[4] In the present study, 14 of 78 children (17.9%) were diagnosed after day 10 of the illness, a relatively lower incidence when compared with the previous study.[4]

We hypothesized that delayed diagnosis of KD might result from patients having younger age, more delayed first physician visit, patients having received more antibiotics for other diagnoses, or an atypical clinical presentation. After analyzing the medical histories and clinical courses of the EDG and DDG group patients, most of these hypotheses were refuted by the study results. Being a patient with younger age was not a significant factor for a delayed diagnosis, and most patients had their first medical visit within 3 days of the onset of illness in both groups. Therefore, most of the patients' parents or caregivers were very vigilant about the fever attacks, and made an early medical visit. Unfortunately, even with a high percentage of early visits on days 1–3 of the illness (76.9%), only 14 patients (17.9%) were diagnosed with KD. Most of the initial diagnoses indicated some signs and symptoms associated with KD. For example, upper respiratory tract infections reflected a mild cough, rhinorrhea and fever. The diagnosis of lymphadenitis, urinary tract infection and scarlet fever reflected lymphadenopathy, pyuria and polymorphous exanthema, respectively. The inaccurate initial diagnoses may have been due to having received an inappropriate treatment. In addition, there have been multiple descriptions in previous literature of patients with KD, but they had an initial diagnosis of cervical adenitis, meningitis, pneumonia, appendicitis, pyelonephritis or retropharyngeal abscess.[8–13] It was interesting to

note that in both the EDG and DDG groups, the medical providers usually focused only on some signs or symptoms associated with KD.

We analyzed the clinical manifestations and laboratory data, but no significant difference between the groups was demonstrated in this study (Tables 1 and 2). However, prolonged fever and higher WBC were demonstrated in the DDG patients and may have resulted from the prolonged course of a systemic inflammation. The higher level of serum IgG in the DDG patients has not been mentioned in other reports, and further study to explain this is necessary. Our results differed from the study in Denver in which fever, rash or platelet count were strong predictors of KD in DDG children.[14]

We considered that with the close clustering of symptoms in the EDG patients, the patients had returned earlier or more frequently for medical attention, which helped the doctors recognize a diagnosis of KD. On the other hand, not only the statistical difference of a delayed onset of signs (mucosa change, skin rash, conjunctivitis) in the DDG patients, but also this timeline model, suggested that the dispersion of the symptoms may have been a factor in late diagnosis. Due to most patients having had the first medical visit after a fever attack, but without appearance of any other KD signs, it is important to advise that patients should return if there is any persistent fever or appearance of any other signs.

There were similar observations in other previous studies.[15–17] Children < 1 year old with KD are significantly more likely to develop coronary artery abnormalities than older children. In both groups, the percentage of males with KD was higher than the percentage of females, and that was compatible with the results of a general report. A delayed diagnosis was harmful in patients because there was a higher possibility of developing coronary abnormalities in DDG than in EDG patients (42.9% *vs.* 14.1%; $p = 0.036$). It is reasonable to hypothesize that prolonged and untreated inflammation may put DDG patients at higher risk for coronary artery involvement.

This study does have several weaknesses and biases that we should illustrate. Due to having only a small group of DDG patients, there may not have been a large enough group to demonstrate any statistical significance for the clinical comparison. We underestimated the methods of use of IVIG (2 g/kg/dose × 1 dose or 400 mg/kg/day × 5 days), duration of aspirin prescribed and primary care provider's specialty in this study. These above weaknesses may have influenced and masked the results of the real observations in this study.

In conclusion, our study showed that 17.9% of the children with KD were diagnosed after the 10th day of illness and were associated with higher WBC and IgG levels. DDG patients exhibited a more dispersed and late onset of the clinical features of KD as compared with EDG patients, in whom symptoms and signs appeared in clusters. A higher percentage of DDG patients and patients younger than 1 year developed coronary artery abnormalities. It is necessary to develop a diagnostic test for KD and to provide more education to health care providers for early recognition of KD.

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