RESEARCH PAPER

Clinical Characteristics of Kawasaki Disease According to Age at Diagnosis

SEONG HYUN KIM, KI HWAN KIM AND DONG SOO KIM

From Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, Seoul, Korea. Correspondence to: Dr Dong Soo Kim, Severance Children's Hospital, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. dskim6634@yuhs.ac
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Objective: We compared the clinical, laboratory and diagnostic features of Kawasaki disease (KD) in children ≤6 mo and ≥5 y of age to those in the more typical age range at diagnosis (6 mo-5 y of age).

Study design: Retrospective analysis.

Setting: Severeance Children Hospital attached to a Medical School, Korea.

Methods: All children with a discharge diagnosis of KD at Severance Children's Hospital (2006-2007) were retrospectively reviewed and grouped according to age at presentation in 3 groups: <6 mo, 6 mo-5 y and ≥5 years. Clinical, hematological, and biochemical features and involvement of coronary artery and proportion of Classic *vs.* Incomplete KD were compared between the 3 groups.

Results: A total of 185 children were identified. Complete KD was found in 63 (34%) children and Incomplete KD in 122 (66%). There was 22(12%) children below 6 months of age, 131 (71%) between 6 months to 5 years) and 32 (17%) above 5 years of age. Clinical, hematological and biochemical features were comparable between the three age groups. Overall, coronary artery lesions occurred in 9% children without any preference for age. The proportion of Classical *vs.* Incomplete KD was also similar in the three age categories.

Conclusion: The clinical and laboratory phenotype of KD does not vary significantly with age.

Key Words: *Age, Clinical features, Kawasaki disease, Korea.*

Kawasaki disease (KD) is an acute, self-limited systemic vasculitis of unknown etiology that occurs predominantly in infants and young children and was first described in 1967 by Tomisaku Kawasaki(1-3). Though its incidence varies among countries, higher rates of KD have been reported in Asian countries such as Japan and Korea(5-7). According to a recent nationwide epidemiologic study, the number of Korean children with KD has steadily increased each year with an annual incidence of 105/100,000 children, which is second only to Japan(8).

KD is the leading cause of acquired heart disease in childhood, causing overt damage in up to 15-25% of untreated children and 2-4% of those who receive appropriate treatment, and may lead to myocardial infarction, sudden death, or ischemic heart disease(2,4,9-12). Prompt diagnosis using intravenous immunoglobulin (IVIG) can reduce the incidence of coronary artery abnormalities from 20-25% to 5%(13,14). Reported risk factors for coronary artery lesions include delayed diagnosis(15,16) and an age of onset outside the typical age distribution(17,18). Some studies have shown that risk factors for delayed diagnosis include an age of < 6 mo and incomplete KD(16). In addition, more patients are being diagnosed who do not meet the classic diagnostic criteria(19). It has been reported that in incomplete KD and younger children, the clinical features are fewer and more subtle and consequently, diagnosis may be more difficult and delayed(16).

Although conventional diagnostic criteria are useful in preventing overdiagnosis, some studies

suggest that these should be revised to include guidelines that recognize incomplete forms of KD(2,20), and a revision of new diagnostic guidelines has been attempted(21,22). General pediatricians may hesitate to make an early diagnosis and treat those outside the typical age range (≤6 mo and ≥5 y of age) and those who do not fully meet the classic criteria. This may delay diagnosis and prompt treatment, and worsen outcome, as discussed above(23). In this study the clinical features, laboratory findings and outcome were compared in patients with KD within and outside the typical age range.

METHODS

A total of 198 patients with KD were treated at Severance Children's Hospital of Yonsei University College of Medicine, Seoul, Korea, between 2006 and 2007. Thirteen cases of recurrent KD were excluded. To investigate age-related differences in clinical characteristics, a retrospective analysis of 185 KD children with a discharge diagnosis of KD was performed after seeking approval from the Institute's Ethics Committee. Diagnosis of KD was made as per AHA Guidelines(2). Subjects were also evaluated to determine whether they satisfied the classic diagnostic criteria. Incomplete KD was defined as meeting less than 4 clinical criteria, irrespective of echocardiography findings(2,24,25). Overall, there were 63 (34%) cases with classic KD and 122 cases with incomplete KD (66%). Subjects were categorized by age in Group A (22 cases, ≤5 mo of age), Group B (131 cases, 6 mo-4 y of age) and group C (32 cases, ≥5 y of age).

All children were treated with IVIG at a dose of 2 g/kg and a high dose of aspirin (100 mg/kg) during the febrile period, in keeping with current consensus guidelines(3,4). Additional IVIG (2 g/kg) was given when fever persisted for more than 48 h, even after the initial IVIG infusion.

Echocardiography was performed within 2 wk of the onset of illness, during the 4th wk, and subsequently repeated depending on the initial findings. Coronary artery lesion (CAL) was defined as an internal lumen diameter >3 mm in children <5 y of age or >4 mm in children ≥5 y of age, if the internal diameter of a segment measured ≥1.5 times that of an adjacent segment, or if the lumen was clearly irregular (the Japanese Ministry of Health criteria)(26). When a coronary artery was larger than normal (dilated) and without a segmental aneurysm, the vessel was considered ecstatic(2). All patients underwent laboratory investigations for leukocyte (WBC) count, hemoglobin, thrombocyte, C-reactive protein, erythrocyte sedimentation rate, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase (CK), CK-MB, N-terminal fragment of B-type natriuretic peptide (NT-proBNP), and urine WBC, which were performed at admission and 1 day after the initial IVIG infusion, in keeping with normal clinical practice at our hospital.

Statistical analysis was performed using SPSS 13.0 for Windows. The three age groups were compared for clinical characteristics including presence of coronary artery lesions, hematological and bio-chemical parameters, and for presence of classical or incomplete KD. The means of the continuous variables in the 3 age groups were compared using 1-way ANOVA. If there were significant differences among the 3 groups, identification of the 2 groups that showed significant differences were made by *post hoc* tests (Scheffe, LSD and Tukey's). Chi-square test was used for comparing categorical variables. A probability of ≤0.05 was considered statistically significant.

RESULTS

The average age of 185 children with KD was 2.8 year, with a range of 1 month to 10 years. The clinical features are summarized in ***Table* I**. The most common clinical feature was fever, followed by red lips and red eyes.Sixty-three of 185 (34%) children fulfilled the diagnostic criteria for Classical KD and 122 (66%) were diagnosed with Incomplete KD. Incomplete KD was found in 15 (68%) children in Group A, 88 (67%) in Group B, and 19 (59%) in Group C (P>0.05).

Laboratory findings between the three age groups are compared in ***Table* II.** Marked leukocytosis and thrombocytosis on admission were noted more in children <6 months of age**.** The

TABLE I CLINICAL CHARACTERISTICS OF KAWASAKI DISEASE ACCORDING TO AGE AT DIAGNOSIS

	Group A ≤5 mo (*n* = 22)	Group B 6 mo-4 y (*n* = 131)	Group C ≥5 y (*n* = 32)	*P*-value
Mean age (mo)	3.5	27	78	0
Male/female	11/11	73/58	13/19	NS
Fever duration(d, mean ± SD)	4.73 ± 3.14	4.91 ± 4.13	6.69 ± 5.82	NS
Clinical signs (%)				
Skin rash	14 (64)	87 (66)	17 (53)	NS
Cervical nodes	7 (32)	47 (36)	17 (53)	NS
Red eyes	15 (68)	95 (73)	23 (72)	NS
Red lips	19 (86)	103 (79)	28 (88)	NS
Changes in extremities	8 (36)	58 (44)	14 (44)	NS
BCG erythema	16 (73)	44 (34)	1 (3)	0.001
Anal desquamation	1 (5)	15 (12)	2 (6)	NS
GB hydrops	4 (20)	15 (13)	2 (8)	NS

NS: *not significant*, *GB*: *gallbladder*.

incidence of sterile pyuria was 14% (26 cases overall: 2 in group A, 20 in group B, and 3 in group C) with statistical insignificance between groups (*P*=0.16). The incidence of coronary artery lesions was comparable both at admission and 6 months later, in all age groups (***Table* III**). The overall recurrence rate was 0.3% with no significant differences between groups (*P*=0.5:1 case in group A, 5 in group B, and none in group C).

DISCUSSION

There have been many reports of the different features of KD outside the typical age range of the disease. In some studies, patients <6 mo of age were at increased risk for CALs, giant aneurysms, incomplete KD, and atypical features(17,27). Other studies have shown that older children and adolescents with KD were predominantly male, had delayed diagnosis of KD, higher incidence of cervical lymphadenopathy, and presence of additional symptoms such as abdominal and joint pain as well as higher rates of CAL(18,23,28,29).

We did not observe any variation in the clinical presentation of children at various ages, except that the erythema at BCG site was more pronounced in children <6 months. In laboratory parameters, leucocytosis and thrombocytosis were more prominent in younger infants. However, the incidence of incomplete Kawasaki disease and coronary artery lesions remained comparable at all ages. The major strength of this study is a large sample size analyzed in different age groups. However, most of the children (66%) had incomplete Kawasaki disease.

While children outside the typical age range (<6 mo and >5 y) are reported to be at higher risk for CALs in some reports (23,27,29), CALs occurred equivalently in all age groups in this study, suggesting that the risk of CAL may not be increased in those who receive early IVIG therapy. Initially, the incidence of CAL was 9% overall in this study, which was similar to other reports, but showed a decreased rate of incidence of 5% on 6-month follow-up echocardiography, as compared to other studies. This may be due to earlier echocardiography performed within the first week of disease onset, unlike in other studies. There were no other cardiac manifestations presenting as heart failure, which may explain the elevated NT-proBNP. However, we found that 7 (4%) cases had pericardial effusion on echocardiography, though it is not a CAL category.

With no specific diagnostic test for KD, physicians are likely to diagnose it on the basis of clinical findings. Rigorous application of the

TABLE II LABORATORY FINDINGS OF KAWASAKI DISEASE BEFORE IVIG TREATMENT

	Group A (*n* = 22)	Group B (*n* = 131)	Group C (*n* = 32)	*P* value
WBC ($x10^3/mm^3$)	16.1 ± 6.1	12.8 ± 5.5	10.4 ± 3.9	0.001
Hemoglobin (g/dL)	15.5 ± 2.6	12.5 ± 0.9	11.9 ± 0.9	NS
Platelet count ($x10^3/mm^3$)	511 ± 304	385 ± 137	331 ± 136	0.01
ESR (mm/h)	47 ± 34.7	54 ± 38.4	50 ± 35.0	NS
CRP (mg/dL)	5.1 ± 4.7	5.7 ± 6.4	6.1 ± 6.2	NS
AST (IU/L)	56 ± 64.5	104 ± 209.0	48 ± 56.8	0.045
ALT	40 ± 42.2	99 ± 164.0	35 ± 75.3	0.09
LDH (IU/L)	517 ± 88.2	615 ± 202.2	501 ± 180.1	0.03
CK (IU/L)	77 ± 65.2	129 ± 172.3	180 ± 326.8	NS
MB (ng/mL)	3 ± 1.3	4 ± 2.1	4 ± 4.1	NS
MB/CK	6 ± 3.3	5 ± 3.2	5 ± 7.5	NS
NT-proBNP (pg/mL)	1203 ± 959.6	1257 ± 3795.3	632 ± 1864.3	NS
Urine WBC	0	0.02 ± 0.14	0.07 ± 0.26	NS

NS: not significant; WBC: White blood cells; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CK: Creatine Kinase; MB: Creatine kinase - MB components; NT: ProBNB: N-terminal fragment of B-type natriuretic peptide.

TABLE III CORONARY ARTERY LESIONS IN KAWASAKI DISEASE

	Group A (*n* = 22)	Group B (*n* = 131)	Group C (*n* = 32)	Total	*P* value
Initial CALs (%)	3 (1.6%)	13 (7.0%)	1 (0.5%)	17 (9.2%)	0.74
F/U CALs (%)	3 (1.6%)	6 (3.2%)	1 (0.5%)	10 (5.4%)	0.15

CALs: *coronary artery lesions, F/U*: *follow up.*

classical clinical diagnostic criteria is inappropriate and may result in missed diagnoses(2). Since some clinical and laboratory findings are characteristic, they can help prevent misdiagnosis(20). BCG site change and NT-proBNP may be highly suggestive markers for acute KD to differentiate from other acute febrile illnesses and also be useful as additional diagnostic tools(30). Recently published less stringent diagnostic algorithms may prove particularly useful, especially in younger age groups(2,22). Further research is needed to continue the revision of diagnostic criteria of the Kawasaki disease.

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WHAT IS ALREADY KNOWN?

- Kawasaki disease is associated with coronary artery lesions; this might be related to the age at which the disease occurs.

WHAT THIS STUDY ADDS?

- In 185 children diagnosed with Kawasaki disease (Classical: 63; imcomplete: 122), there were no major differences in clinical presentation with respect to age, including the incidence of coronary artery lesions.

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