Affects of “Age at Diagnosis” on Coronary Artery Lesions in Patients With Incomplete Kawasaki Disease

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ABSTRACT

Background and Objectives: Diagnosis of Kawasaki disease (KD) is based on 5 clinical features. Incomplete KD (IKD), which has fewer features, is more common in infants and older children, in whom the rate of coronary artery aneurysms is paradoxically higher. We conducted this study to evaluate risk factors associated with age-at-diagnosis on coronary arterial lesions (CAL) in patients with IKD.

Subjects and Methods: Retrospective data from 396 patients with KD in a single center were collected from January 2003 to July 2007. Patients were grouped according to their age at diagnosis; Group A (<1 year of age), Group B (1 ≤ age < 5 years of age), and Group C (≥ 5 years of age).

Results: Among a total of 396 patients with KD, 87 (22.0%) were in Group A, 246 (62.1%) in Group B, and 63 (15.9%) in Group C. In groups A and C, lag times for starting intravenous immunoglobulin (IVIG) were longer than in Group B. There were no differences in the incidence of IKD, late CAL, or rates of IVIG retreatment among the three groups. Among 174 patients with IKD, there were no age-related differences in late CAL incidence or IVIG retreatment. Compared with typical KD, duration of fever and lag times to start IVIG were longer, and the rate of IVIG retreatment was higher in IKD, but there was no difference in the risk of CAL between typical KD and IKD.

Conclusion: In the management of KD, especially the incomplete type, age-associated factors appear not to be significant for predicting the development of CAL.

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KEY WORD: Mucocutaneous lymph node syndrome.

Introduction

Kawasaki disease (KD) is an acute febrile vasculitis of unknown etiology. It is a major cause of pediatric acquired heart diseases in Asia including South Korea.1,2 According to epidemiologic studies of KD in Korea from 2003 to 2005, 87.7% of cases occur in children under 5 years of age. The peak age of onset was 6-12 months of age with the highest frequency being 13.9%.3 For children in the acute phase of KD, treatment with intravenous immunoglobulin (IVIG) and aspirin is still recommended by the American Heart Association (AHA). Approximately 15% to 25% of untreated children develop coronary artery aneurysms or ectasia, but treatment with IVIG in the acute phase reduces this risk to below 5%.4 Diagnosis of KD is based on 5 clinical features. It can be difficult to diagnose because there is no unambiguous diagnostic laboratory test. Some patients who don’t fulfill the criteria have been diagnosed as having “incomplete” KD, more frequently in infants and children older than 5 years of age, and diagnosis of KD might be delayed if there are fewer clinical features, which can lead to an increased incidence of coronary complications.5-10

In the present study, we evaluated and compared the prevalence, clinical features and time to start IVIG, and outcomes among different age groups, and analyzed age-associated risk factors for coronary arterial lesions (CAL) in patients with incomplete KD (IKD).

Subjects and Methods

The charts of 396 inpatients diagnosed with KD at
A total of 396 patients with KD and 174 with IKD were analyzed. The clinical profiles for the three groups are shown in Table 1. The number of males, 271 (69%), was greater than the number of females, 125 (31%), and the male-to-female ratio was 2.17 : 1. The mean age at diagnosis was 33.70 ± 24.38 months (range: 2 months-12 years).

Eighty-seven (22.0%) were in Group A, 246 (62.1%) in Group B, and 63 (15.9%) in Group C. The mean age of each group was 7.23 ± 2.49 months in Group A, 32.23 months in Group B, and 24.38 months in Group C. The IVIG retreated rate was 0.90% in Group A, 2.17% in Group B, and 7.10% in Group C. The mean age at KD diagnosis was 33.70 ± 3.89 months in Group A, 24.38 ± 2.49 months in Group B, and 24.38 ± 2.49 months in Group C. The mean WBC count was 11.59 ± 3.89 × 10^3/μL in Group A, 14.00 ± 1.91 × 10^3/μL in Group B, and 13.11 ± 0.34 × 10^3/μL in Group C. The mean Hb was 11.78 ± 1.10 g/dL in Group A, 14.31 ± 0.51 g/dL in Group B, and 13.31 ± 0.28 g/dL in Group C. The mean CRP was 4.97 ± 5.52 mg/dL in Group A, 3.79 ± 0.47 mg/dL in Group B, and 3.79 ± 0.47 mg/dL in Group C. The mean IVIG retreated rate was 0.90% in Group A, 2.17% in Group B, and 7.10% in Group C.

Results

Demographic characteristics and initial laboratory findings

A total of 396 patients with KD and 174 with IKD were reviewed retrospectively. Clinical profiles, initial laboratory data, echocardiographic findings, therapeutics and follow-up data in patients with KD were collected from each medical record. These patients were divided into 3 groups according to the age at diagnosis: infants (Group A), children 1 year of age or older but younger than 5 years of age (Group B), children 5 years-old or older (Group C).

Diagnosis of KD was based on clinical features using the revised criteria of the AHA. This included fever for at least 4 days and an additional four of the following five signs: bilateral conjunctival injection, oral desquamation,草莓 tongue, changes in hands and feet (strawberry tongue); changes, such as injected pharynx, dry cracked lips, or strawberry tongue; changes in hands and feet, such as redness and swelling in the acute phase, and periungual desquamation in the subacute phase; rash, primarily on the trunk, that may be maculopapular, or erythema multiforme; and a cervical lymph node greater than 1.5 cm in diameter. Even if the aforementioned clinical criteria were not satisfied, we included patients with dilatation or aneurysm of the coronary artery on echocardiography. Diagnosis of IKD was defined as unexplained fever for ≥4 days associated with 2 or 3 of the principal clinical features, or as unexplained fever for only a few days with 4 of the typical symptoms listed above, and exclusively other diseases.

Echocardiograms were usually repeated on admission, again 2 months after the first echocardiogram, and thereafter whenever necessary. Normal ranges for age-specific coronary artery size were used following the criteria of the AHA. Based on these echocardiographic measurements of coronary arteries, cases were classified as abnormal when the internal lumen diameter was ≥3 mm in children younger than 5 years of age or ≥4 mm in children aged 5 years or more, or when the internal diameter of any segment measured at least 1.5 times that of an adjacent segment, or when the coronary artery lumen was clearly irregular.

Mean, SD and range were calculated for all descriptive variables. Nominal data were analyzed using the χ^2 test. Continuous variables were compared using analysis of variance. P < 0.05 was considered statistically significant. Analyses were done using Statistical Package for the Social Sciences (SPSS) 13.0 (SPSS Inc, Chicago, IL, USA).

Table 1. Demographic features and initial laboratory and outcome-related findings among the three age groups with Kawasaki disease (KD) (n=396)

|                          | Total    | Group A (age<1 year) | Group B (1≤ age<5 years) | Group C (age ≥ 5 years) | P   |
|--------------------------|----------|----------------------|--------------------------|-------------------------|-----|
| Number of patients (%)   | 396 (100)| 87 (22.0)            | 246 (62.1)               | 63 (15.9)               | -   |
| Age at KD diagnosis (month) | 33.70 ± 24.38 | 7.23 ± 2.49          | 32.23 ± 13.05            | 76.02 ± 17.16           | 0.00|
| Male : Female ratio      | 2.17 : 1 | 2.35 : 1             | 2.00 : 1                 | 2.70 : 1                | 0.58|
| Incomplete KD (no, %)    | 174 (43.9)| 38 (31.4)           | 102 (48.1)               | 34 (64.7)               | 0.11|
| Initial laboratory findings |          |                      |                          |                         |     |
| Hemoglobin (g/dL)        | 11.52 ± 1.25 | 11.16 ± 1.31          | 11.59 ± 1.25             | 11.78 ± 1.10            | 0.01|
| Hematocrit (%)           | 33.66 ± 3.76 | 32.68 ± 3.78          | 33.80 ± 3.75             | 34.51 ± 3.51            | 0.01|
| WBC count (10^3/μL)      | 14.13 ± 6.45 | 15.01 ± 6.00          | 14.00 ± 6.35             | 13.31 ± 7.26            | 0.28|
| Platelets (10^3/μL)      | 384.51 ± 158.28 | 449.06 ± 171.10  | 375.00 ± 154.59          | 326.46 ± 119.72         | 0.00|
| Albumin (g/dL)           | 3.87 ± 0.45 | 3.89 ± 0.41           | 3.89 ± 0.47              | 3.79 ± 0.47             | 0.34|
| CRP (mg/dL)              | 6.32 ± 6.09 | 7.65 ± 6.05           | 6.35 ± 6.70              | 4.97 ± 5.52             | 0.05|
| Outcome-related findings |          |                      |                          |                         |     |
| Febrile duration (days)  | 4.88 ± 2.03 | 4.80 ± 2.39           | 4.92 ± 1.94              | 4.83 ± 1.90             | 0.88|
| Days before starting IVIG (days) | 1.60 ± 1.47 | 1.85 ± 1.78          | 1.43 ± 1.26              | 1.91 ± 1.69             | 0.03|
| Initial CAL (no, %)      | 136 (34.3) | 25 (28.7)            | 103 (41.9)               | 8 (12.7)                | 0.00|
| F/u 2 months CAL (no, %) | 44 (11.1) | 10 (11.8)           | 30 (12.9)                | 4 (6.6)                 | 0.39|
| IVIG retreated (no, %)   | 90 (22.7) | 16 (21.7)            | 65 (30.8)                | 9 (16.9)                | 0.32|
| Add steroids after       |          |                      |                          |                         |     |
| IVIG retreated (no, %)   | 28 (7.1) | 8 (10.8)            | 16 (7.5)                 | 4 (7.5)                 | 0.67|

Values in the table are mean ± standard deviation. WBC: white blood cell, CRP: C-reactive protein, IVIG: intravenous immunoglobulin, CAL: coronary arterial lesion, F/u: follow up.
± 13.05 months in Group B, and 76.02 ± 17.16 months in Group C. Group A had significantly higher platelet counts and lower hemoglobin values than the other groups.

The IKD group (n = 174) accounted for 43.9% of total patients (n = 396), with 38 (51.4%) in Group A, 102 (48.1%) in Group B, and 34 (64.7%) in Group C. Groups A and C had relatively higher proportions of the incomplete type than Group B (p = 0.11).

Response to treatment and development of coronary arterial lesions
Every patient with KD received high-dose IVIG treatment or more. The mean lag time to start IVIG after admission was significantly longer in Groups A and C (1.85 ± 1.78 days and 1.91 ± 1.69 days, respectively) than in Group B (1.43 ± 1.26 days). Initial echocardiography findings indicated that there was a higher incidence of CAL in the 103 patients (41.9%) in Group B. After 2 months, there were no significant differences among the 3 groups.

There were no significant differences among the 3 age groups with regard to the necessity for IVIG retreatment or additional dexamethasone (Table 1).

Clinical features and outcomes in patients with incomplete Kawasaki disease
Comparisons of clinical features among the 3 age groups with incomplete Kawasaki disease (IKD) are shown in Table 2. The male-to-female ratio was 2.0 : 1. The mean age at diagnosis was 35.14 ± 25.11 months.

The lag time to start IVIG after admission were relatively longer in Groups A and C than Group B (p = 0.29). Duration of fever, however, was not different among the 3 groups.

On initial echocardiography, there was a higher incidence of CAL (n = 43, 42.2%) in Group B. After 2 months, there were no significant differences among the 3 groups. There were no significant differences among the 3 groups with regard to the need for IVIG retreatment or for additional dexamethasone (Table 2).

Comparisons among the 3 IKD groups with regard to common clinical features are described in Table 3. Most common symptoms in the 3 IKD groups were bilateral conjunctival injection (38% in Group A), red lip/oral mucosal changes (38.3% in Group B), and cervical lymphadenopathy (34.4% in Group C).

Age-specific comparisons of clinical features and outcomes between patients with typical Kawasaki disease and those with incomplete Kawasaki disease
Compared with typical KD, the duration of fever was longer in IKD Group A, but there were no significant differences for other parameters.

In IKD Group B, the duration of fever and lag time to start IVIG after admission were longer and the rate of IVIG retreatment higher than those with typical KD. There were no differences in CAL between KD and IKD groups (Table 2).

Table 2. Clinical features and outcomes among the three age groups with incomplete Kawasaki disease (IKD) (n = 174)

|                          | Total | Group A (age<1 year) | Group B (1 ≤ age<5 years) | Group C (age ≥ 5 years) | p   |
|--------------------------|-------|----------------------|---------------------------|------------------------|-----|
| Number of IKD patients (%) | 174 (100) | 38 (21.8)          | 102 (58.7)               | 34 (19.5)              | 0.11 |
| Age at KD diagnosis (months) | 35.14 ± 25.11 | 7.39 ± 2.55       | 32.24 ± 13.40            | 74.88 ± 14.43*         | 0.00 |
| Male : Female ratio       | 2.00 : 1 | 1.53 : 1*           | 1.91 : 1                 | 3.25 : 1               | 0.34 |
| Outcome-related findings  |       |                     |                          |                        |     |
| Febrile duration (days)   | 5.11 ± 2.26 | 5.39 ± 2.71*       | 5.22 ± 2.23*             | 4.50 ± 1.71            | 0.19 |
| Days to start IVIG (days) | 1.78 ± 1.64 | 2.03 ± 1.78        | 1.62 ± 1.55*             | 2.00 ± 1.74            | 0.29 |
| Initial CAL (no, %)       | 59 (33.9) | 10 (26.3)           | 43 (42.2)                | 6 (17.6)               | 0.02 |
| F/u 2 months CAL (no, %)  | 27 (16.4) | 7 (18.4)            | 16 (16.8)                | 4 (12.5)               | 0.79 |
| IVIG retreated (no, %)    | 46 (26.6) | 10 (26.2)           | 27 (26.7)*               | 9 (26.5)               | 0.63 |

Mean ± standard deviation. *There were significant differences between complete and incomplete KD (p<0.05). WBC: white blood cell, CRP: C-reactive protein, IVIG: intravenous immunoglobulin, CAL: coronary arterial lesion

Table 3. Most common symptoms in incomplete Kawasaki disease among the three age groups

| Order of frequency | Group A (%) | Group B (%) | Group C (%) |
|-------------------|-------------|-------------|-------------|
|                   | n = 38      | n = 102     | n = 34      |
| Most common       | Conjunctival injection (38.0) | Oral mucosal changes (38.3) | Cervical lymphadenopathy (34.4) |
| 2nd most common   | Polymorphous skin rash (20.1) | Conjunctival injection (26.9) | Conjunctival injection (24.6) |
| 3rd most common   | Oral mucosal changes (18.3) | Polymorphous skin rash (16.1) | Oral mucosal changes (18.9) |
| 4th most common   | Change of extremities (14.6) | Cervical lymphadenopathy (11.3) | Polymorphous skin rash (16.3) |
| 5th most common   | Cervical lymphadenopathy (8.9) | Changes in the extremities (7.7) | Changes in the extremities (5.8) |
Discussion

KD is an acute febrile vasculitis of unknown etiology that commonly affects children under 5 years of age. Since first reported by Tomisaku Kawasaki in 1967, it has been the most common acquired cardiovascular disease among pediatric patients. In 1984, Furusho et al. reported the effects of IVIG therapy on KD, and the occurrence of CAL and its mortality were significantly reduced.

Whereas children with the typical KD are immediately diagnosed and given IVIG treatment after admission, however, children with IKD are difficult to distinguish from children with other infectious diseases and the time required to find clear diagnostic criteria often results in delayed treatment of KD. There was a greater time interval from meeting the diagnostic criteria to making the diagnosis, and a higher proportion of CAL in infants under 1 year of age and children over 5 years of age compared with children 1 to 5 years of age. The Kawasaki Disease Research Committee published a set of revised diagnostic criteria in 2002. Major alterations were interpretation of cases with 4 or fewer febrile days shortened by early IVIG treatment and the importance of IKD. Then, the AHA published the latest set of diagnostic criteria and the importance of IKD was emphasized. Conventional diagnostic criteria should be viewed as guidelines that are particularly useful in preventing over-diagnosis, but may also result in failure to recognize incomplete forms of the illness. In the present study, according to the revised guidelines of the AHA, children under the age of 1 year and over 5 years with IKD have a higher incidence (51.4% and 64.7%, respectively) compared with KD (22.0% and 15.9%, respectively). Moreover, time to start IVIG treatment after admission was significantly longer in both younger and older IKD groups than in children 1 to 5 years of age. Since there is a possibility of delayed treatment in both groups, the risk of CAL accompanying IKD may be increased. In our study, however, there was no significant difference among the 3 groups between KD and IKD.

Even if a patient has only a few KD symptoms, suggesting IKD, early diagnosis of KD can be achieved through common clinical manifestations that distinguish among the 3 groups by age. Hsiao et al. reported that patients less than 6 months of age with oral lesions or hard swelling of the palms or feet, are rare. Typical mucosal changes and enlarged lymph nodes in patients less than 6 months old are less likely. Fan et al. reported that cervical lymph node enlargement appeared in most school children with KD who were diagnosed early with acute purulent lymph nodes and treated with antibiotic treatment. In our study of IKD, bilateral conjunctival injection was the most common presentation of diagnostic criteria in infants and cervical lymphadenopathy in patients older than 5 years.

Recent studies of vascular function in KD have focused on endothelial dysfunction and the progressive atherosclerosis after the onset of KD. They suggest that there are no significant differences between normal coronary arteries of well-treated KD patients and healthy people. Even in KD patients with good responses to IVIG, CAL still occasionally occurs. High echodensity of the coronary arterial wall was demonstrated at a mean of 5.4 days from onset. Without IVIG therapy, diffuse coronary artery dilatation was observed in 50% of KD patients at about 9.5 days after onset of symptoms, diffuse coronary artery dilatation progresses to aneurysms in 28.8% by 11.4 days, and resolution of coronary artery dilatation occurs within 30 days of onset of transient dilation. CALs that persist beyond 30 days from onset might be considered KD sequelae. Therefore, serial echocardiographic studies should be performed to evaluate CAL.

We found that children older than 5 years of age as well as those younger than 1 year of age have a higher percentage of IKD, and there were no significant differences in clinical outcomes whether re-treatment was needed or not, and whether there is advanced development of late CAL. Prolonged fever without any definite association with conjunctival injection in children younger than 1 year of age and cervical lymphadenopathy in children older than 5 years of age should be considered as diagnostic for KD. Recently in the management of KD, especially IKD, age at diagnosis may be no more significant to determine the development of CAL.

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