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Original Article

Kawasaki disease in infants three months of age or younger

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Background and Purpose: Kawasaki disease (KD) is rare in infants ≤3 months of age. This study analyzed the features of KD in 25 infants ≤3 months of age treated from February 1994 to December 2004.

Methods: Basic characteristics, clinical, laboratory, echocardiographic, therapeutic, and follow-up data of the infants were obtained from chart records.

Results: There were 19 male and 6 female infants in this cohort. The frequency of the 5 principal clinical features was as follows: changes in lips and oral cavity, 84%; bilateral bulbar conjunctival injection without exudates, 80%; polymorphous exanthem, 68%; cervical lymphadenopathy, 28%; and changes in extremities, 24%. Six infants (24%) fulfilled criteria for KD including fever which persists for 5 or more days with at least 4 of the principal clinical criteria, and the remaining infants were classified as having incomplete KD (all of whom showed coronary involvement). Coronary artery dilatation was found in 20 infants (80%). One infant developed a medium-size aneurysm (5.2 mm), while the others had only coronary arterial ectasia or small aneurysms. Coronary artery aneurysms regressed within 1-year follow-up in all but one infant. No fatal or recurrent case was observed during the study period.

Conclusions: Infants ≤3 months of age with KD usually presented with incomplete clinical features. A high proportion of coronary artery involvement was observed in this series. Echocardiography should be considered in very young infants with unexplained prolonged fever who do not present all of the principal clinical features of KD.

Key words: Coronary aneurysm, disease progression, infant, mucocutaneous lymph node syndrome, newborn infant

Introduction

Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown cause, predominately affecting children under 5 years of age. KD is characterized by fever, bilateral non-exudative conjunctivitis, erythema of lip and oral mucosa, cervical lymphadenopathy, changes in the extremities and polymorphous exanthem. Coronary artery ectasia or aneurysms occur in about 20% of untreated patients and may cause ischemic heart disease and sudden death [1,2]. The peak age incidence of KD varies with different countries and is in the first year of life in Japan and Taiwan [3,4]. Although infants have the highest incidence of KD, it is rare in young infants ≤3 months of age [5]. The diagnosis of KD in young infants is challenging because of its rarity and high incidence of incomplete presentation. This study analyzed the clinical presentations and outcomes of KD in infants ≤3 months of age.

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Methods

We retrospectively reviewed the characteristics of infants ≤3 months of age with KD treated in Chang Gung Children's Hospital (CGCH) from February 1994 to December 2004. Basic characteristics, clinical, laboratory, echocardiographic, therapeutic, and follow-up data of the infants were obtained from chart records. KD was diagnosed based on the symptom of fever persisting for 5 or more days with at least 4 of the following 5 principal clinical criteria: 1) bilateral bulbar conjunctival injection without exudate; 2) changes in lips and oral cavity; 3)

Table 1. Basic characteristics and laboratory data of infants ≤3 months of age with Kawasaki disease

	Mean	Median	Minimum	Maximum
Age (days)	73.9	75	45	90
Duration of diagnosis (days)	6.3	5	3	15
Fever post IVIG (days)	2.6	1	1	14
Total fever duration (days)	9.0	8	5	17
WBC count (/mm^3)	18,233	15,900	4900	40,000
Hemoglobulin (g/dL)	9.3	9.4	6.8	13.4
Neutrophils (%)	60.4	59.0	38.0	83.0
Lymphocytes (%)	27.8	26.0	9.0	55.0
Platelet count (/mm^3)	355,000	380,000	4000	527,000
C-reactive protein (mg/L)	124.2	120.0	16.2	289.7

Abbreviations: IVIG = intravenous immunoglobulin; WBC = white blood cell

cervical lymphadenopathy; 4) polymorphous exanthem; and 5) changes in extremities. Incomplete KD was defined as fever for 5 or more days and fewer than 4 of the criteria with coronary involvement [6]. Time needed for diagnosis was defined as the day from the first day of fever to the day when diagnosis was made. Coronary artery abnormality was defined as the internal lumen diameter >2 mm, the internal diameter of a segment ≥1.5 times that of an adjacent segment, or the demonstration of clearly irregular coronary lumen [7,8]. Aneurysms were classified as small (<5 mm, internal diameter), medium (5-8 mm, internal diameter), or giant (>8 mm, internal diameter) [2].

Results

Twenty five infants, including 19 males and 6 females, were identified. They represented 4.1% of the 625 patients with KD treated at CGCH during this period. None of the infants were younger than 28 days old. Six infants were between 29 and 60 days old and 19 infants between 61 and 90 days old. The basic characteristics and laboratory data of the infants are summarized in Table 1. Pyuria was found in 10 of the 20 infants (50%). Six of the 13 infants (46.1%) who underwent a spinal tap showed cerebrospinal fluid pleocytosis and normal glucose and protein levels. Elevation of asparate aminotransferase and alanine aminotransferase was observed in 3 of the 12 (25%) and 2 of the 6 (33%) infants who had these tests, respectively. The clinical features of patients in this series are compared with those of other reported series from Taiwan in Table 2 [9,10]. Six infants (24%) met the criteria for KD while the other 19 (76%) were classified as having incomplete KD. The number and percentage of infants fulfilling each of the diagnostic criteria for KD are shown in Table 3. Intravenous immunoglobulin (IVIG) was administered once the diagnosis was made. Only

Table 2. Comparative analysis of data from three reports on Kawasaki disease in Taiwan

	Tseng et al [9]	Hsieh et al [10]	Present study
Number of patients	48	132	25
Patient age	<12 months	All children	≤3 months
Male gender (%)	60.4	62.1	76.0
Incomplete presentation (%)	31.2	15.0	76.0
Changes in lip and oral cavity (%)	89.6	87.1	84.0
Bilateral bulbar conjunctival injection (%)	89.6	93.9	80.0
Polymorphous exanthema (%)	89.6	86.3	68.0
Changes in extremities (%)	72.9	93.2	24.0
Cervical lymphadenopathy (%)	0	31.1	28.0
Erythema at BCG inoculation site (%)	NR	NR	48.0
Coronary artery dilatation (%)	34.1	35.4	80.0
Leukocytosis (WBC >15,000/mm^3) [%]	<50.0	NR	72.0
C-reactive protein (mg/L)	82.0	NR	124.2
Retreatment rate (%)	NR	3.8	12.5

Abbreviations: BCG = Bacille Calmette-Guérin; WBC = white blood cell; NR = not reported

Table 3. Number and percentage of infants fulfilling each of the diagnostic criteria for Kawasaki disease

	Number of infants (%)
Fever plus 5 criteria	1 (4)
Fever plus 4 criteria	5 (20)
Fever plus 3 criteria	13 (52)
Fever plus 2 criteria	2 (8)
Fever plus 1 criterion	3 (12)
Fever plus 0 criterion	1 (4)

2 infants received IVIG treatment at more than 10 days after fever onset. One infant did not receive IVIG because fever resolved spontaneously when the diagnosis was made. Six patients remained febrile at more than 48 h after IVIG treatment. Three infants failed to respond to initial therapy and were retreated with IVIG.

Coronary arterial lesions developed in 20 infants (80%). Among these infants, left main coronary artery dilatation was found in 9, and both left and right coronary artery dilatation were found in 11. One infant developed medium-sized aneurysm (5.2 mm), and the others all had only coronary arterial ectasia or small aneurysms. Coronary artery aneurysms regressed within 1 year of follow-up in all but one of the infants. No fatal or recurrent case occurred during follow-up.

Discussion

In Taiwan, nearly 90% of KD involved children less than 5 years old. Although the peak age is less than 1 year of age, the annual incidence in infants ≤3 months of age (40.6 per 100,000) was much lower than that in infants 3 to 11 months of age (180.4 per 100,000) [3]. In a study from Japan, infants with KD who were ≤3 months of age represented 1.67% of 105,755 patients and only 6 patients were younger than 30 days of age [11]. There was no neonatal case in this series. Our 25 infants represented 4.1% of all patients with KD treated at CGCH during the study period. The higher incidence of KD in infants ≤3 months of age in this series may be due to the tertiary referral setting of this hospital in northern Taiwan.

The prevalence of incomplete presentation of KD was nearly 15% in a previous study from Taiwan [10]. Incomplete KD is more common in infants than in older children. The prevalence of incomplete KD in infants ranged from 31.2% to 46% in previous studies [9,12]. In this series, the 76% prevalence of incomplete KD was much higher than expected. Only six infants were classified as having all of the principal signs of KD, and more than one-half of infants with incomplete KD presented 3 of the principal criteria. Changes in lips and oral cavity (84%) and bilateral bulbar conjunctival injection (80%) were the most common of the principal criteria met. Changes in extremities (24%) and cervical lymphadenopathy (28%) were the least 2 criteria met. Changes in extremities were relatively infrequent in this series of KD infants ≤3 months of age as compared with those in older children in previous studies [9,10].

Leukocytosis with predominance of granulocyte is a typical laboratory finding in the acute stage of KD. White blood cell (WBC) count >15,000/mm^3 is observed in approximately 50% of patients [6]. Elevation of C-reactive protein (CRP) is nearly universal. A CRP level >100 mg/L indicates a higher risk of recurrence in the first year [13]. Eighteen of our infants had a WBC count >15,000/mm^3, and 13 had a CRP level >100 mg/L. As compared with older children in previous studies [9], active inflammation in infants with KD who were ≤3 months old was more severe, but no recurrent case was found in this series. Thrombocytosis is rarely seen in the first week of the illness, but usually appears in the second week, and peaks in the third week [6]. Ichida et al found that the maximal platelet count was higher in patients with coronary aneurysms [14]. Eleven of the young infants in this study presented with thrombocytosis (platelet count >400,000/mm^3) during the first week of illness. None of them had a platelet count >1,000,000/mm^3 during the follow-up period. However, 80% of these infants had coronary artery involvement. Thrombocytopenia, which is also rarely seen in the acute stage of KD, presented in two of our infants. Both these infants failed to respond to initial IVIG treatment. They also had prolonged fever for more than 10 days and subsequently developed coronary aneurysms. KD patients with thrombocytopenia appear to have a protracted course and increased risk of coronary aneurysm formation [15].

IVIG and aspirin are the two main agents used in treating KD. The mechanism of action of IVIG in treating KD is unknown. A dose-response effect with a higher single infusion dose has been shown to have the greatest efficacy [16,17]. This therapy should be administered within 10 days of symptom onset. Treatment of KD with IVIG within 5 days did not appear more beneficial but it may increase the need for IVIG retreatment [18]. Approximately 10% of patients with KD failed to defervesce with initial IVIG therapy [6]. Twenty four of our infants received IVIG therapy at a

dose of 2 g/kg; most of them were treated with a single-infusion regimen within 10 days. Three infants (12.5%) failed to respond to initial IVIG therapy and developed coronary artery dilatation. This unresponsive rate is similar to previous reports [6,19].

The major sequelae of KD are related to the cardiovascular system, especially the coronary arteries. Since the Japanese Ministry of Health and Welfare defined the criteria for coronary artery abnormalities in KD in 1984 [7], they have been used worldwide in the assessment of coronary abnormalities. However, these criteria do not take into acccount the increase in coronary artery dimensions with body size, which may result in underdiagnosis. These criteria may also underestimate the true prevalence of coronary aneurysms. de Zorzi et al [20] and Kurotobi et al [8] suggested that the criteria should be adjusted for body size and for the coronary anatomical site. According to Kurotobi et al's suggestion, a coronary diameter >2 mm would be considered abnormal in infants ≤3 months of age. Eighty percent of infants in this series showed coronary artery dilatation, which was an extremely high percentage as compared with the series of Tseng et al [9] and Hsieh et al [10].

The very high rate of coronary aneurysms in young infants may be related to the high rate of incomplete presentation in these patients, for whom coronary involvement is essential for the diagnosis of incomplete KD. Coronary artery aneurysms demonstrated regression in approximately 50% of patients within 1 to 2 years after disease onset [1]. Factors positively associated with the regression of aneurysms include smaller aneurysms, age <1 year at onset of KD, fusiform rather than saccular aneurysm morphology, and aneurysm location in a distal coronary segment [21]. All but one of the infants in this series showed regression of aneurysms at follow-up within 1 year and no fatal or recurrent case occurred, indicating a favorable outcome for this specific group of patients.

In conclusion, most infants ≤3 months of age with KD in this series presented incomplete clinical features. A very high proportion of these infants developed coronary artery lesions. Echocardiography should be considered in very young infants with unexplained fever, whether or not the full picture of KD has been presented.

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