Kaohsiung Journal of Medical Sciences (2012) 28, 23–29

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Clinical relevance of the risk factors for coronary artery lesions in Kawasaki disease

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Received 20 December 2010; accepted 2 May 2011
Available online 11 December 2011

KEYWORDS
Coronary artery lesions;
Intravenous immunoglobulin;
Kawasaki disease

Abstract We aimed to investigate which factors are associated with coronary artery lesions (CALs) during the acute and chronic stages in Taiwanese children with Kawasaki disease (KD). A total of 216 children with KD were enrolled. Clinical and laboratory data were obtained for each child within 7 days of illness. The patients were classified into KD children without acute CALs ($n = 135$) and those with acute CALs ($n = 81$) according to echocardiography data at Week 2 after treatment. Then, KD children with acute CALs were further divided into those without chronic CALs ($n = 55$) and with chronic CALs ($n = 26$) according to annual echocardiography data. During acute stage of KD, neutrophil count (<54%) [odds ratio (OR) = 0.44, $p = 0.041$]; second dose of intravenous immunoglobulin (IVIG) treatment (OR = 5.01, $p = 0.009$); and platelet count (≤400,000) (OR = 0.42, $p = 0.006$) were correlated with the risk of acute CALs. During chronic stage of KD, age (12–60 months) (OR = 0.25, $p = 0.042$); first dose of IVIG treatment (OR = 0.12, $p = 0.005$); and band count (≥3%) (OR = 3.51, $p = 0.032$) were correlated with the risk of chronic CALs. Our results suggest that the effects of neutrophil count, doses of IVIG treatment, and platelet count on CALs in acute KD are important. Age, doses of IVIG treatment, and band count are related to the persistence of CALs in chronic stage of KD.

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1607-551X/$36
doi:10.1016/j.kjms.2011.09.002

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis with a predilection for Asian race, which occurs mainly in infants and children younger than 5 years of age [1]. The annual incidence of KD in Taiwan is estimated to be 69/100,000 children, the third highest in the world after Japan and Korea [2–4]. KD is characterized by fever; rash; conjunctivitis; inflammation of the mucous membranes; swollen, erythematous hands and feet; and cervical adenopathy. The etiology remains unknown. Treatment with a single high dose of intravenous immunoglobulin (IVIG) is effective in resolving the acute inflammation and reducing the risk of coronary artery lesions (CALs) [5]. However, KD is liable to be complicated by development of CALs, which develop in approximately 15–25% of untreated KD children and in about 5% of those after IVIG therapy [5,6]. KD seems to be a benign, self-limited illness, but actually it is the leading cause of acquired heart disease in children. This makes how to identify patients at risk of CALs an important issue.

Many previous studies have identified putative predictors of CAL development in KD including demographic, clinical, and laboratory variables. These studies have identified predictors of poor coronary outcome in KD patients, including IVIG resistance, low hemoglobin level, low albumin level, high white blood cell (WBC) count, high neutrophil count, high C-reactive protein (CRP) level, male sex, and age younger than 1 year or older than 6 years [7–12]. In contrast to the aforementioned studies, Honkanen et al [13] found that the degree of anemia, platelet count, erythrocyte sedimentation rate (ESR), and WBC count were not predictive of coronary artery abnormalities.

Thus, controversy still surrounds some clinical and laboratory risk factors for CALs in KD. The purpose of this study was to investigate the association of clinical and laboratory data with CALs in Taiwanese KD children.

Materials and methods

We performed a retrospective cohort study at the Department of Pediatrics, Kaohsiung Veterans General Hospital, Taiwan. Medical records of all children who received a diagnosis of KD in our hospital between 1993 and 2009 were reviewed. Medical records were reviewed for age; sex; presenting symptoms; doses of IVIG treatment (2 g/kg/dose); IVIG brand (Octagam (Octapharma AG; Lachen, Switzerland) from 1993 to 2005, Gamimune (Bayer Corporation; Clayton, NC, USA) from 2005 to 2007, TBSF (CSL limited; Broadmeadows, Victoria, Australia) from 2008 to 2009); complications; and laboratory data, including baseline WBC with differential count (neutrophil, lymphocyte, and band), platelet count, hemoglobin level, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, and CRP level within 7 days of illness. A total of 216 children who met the established criteria of acute KD were enrolled [1]. IVIG resistance was defined as persistent fever for 3 days after initial IVIG. Then, a second dose of IVIG (2 g/kg/dose) was administered. All KD children underwent two-dimensional echocardiography at the time of diagnosis and again at Week 2, Week 4, and Week 8 after treatment, and annually in follow-up. The internal diameter of the coronary arteries was measured and CALs were defined as follows: coronary arteries were classified as abnormal if the internal lumen diameter was $\geq$3 mm in children younger than 5 years or $\geq$4 mm in children older than 5 years, if the internal diameter of a segment measured 1.5 times that of an adjacent segment, or if the coronary lumen was clearly irregular [14]. The patients were divided into two groups: those who had no acute CALs and those who had acute CALs. Those with acute CALs were further divided into two groups: those without chronic CALs and those with chronic CALs. Acute CALs were defined as CALs at Week 2 after treatment in the acute stage, and chronic CALs were defined as CALs that persisted for 1 year in the chronic stage. Two senior pediatric cardiologists assessed the images independently. For evaluation of intra- and interrater reliabilities, a random sample of 40 patients' measurements was taken twice on different occasions. Kappa coefficients were 0.943 ($p < 0.001$) and 0.914 ($p < 0.001$) for intra- and interrater reliabilities, respectively. The reliability of band count was assessed by six laboratory technicians to check 40 different blood samples. Kappa coefficients were 0.958 ($p < 0.001$) and 0.939 ($p < 0.001$) for intra- and interrater reliabilities of band count, respectively. This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital.

Statistical analysis

All data are expressed as mean $\pm$ standard deviation. Demographic and clinical data between patients with/without CALs were compared by the Chi-square test or Student *t* test. The variables associated with CALs were then included in a multivariate logistic regression model. A *p* value <0.05 was considered statistically significant. The statistical software package of SPSS (version 12.0; SPSS Inc., Chicago, IL, USA) was used for all of the statistical analysis.

Results

A total of 216 patients who met the criteria for inclusion were reviewed. They were studied at a mean follow-up duration of 5.8 ± 5.1 years after KD. There were 84 girls and 132 boys with a mean age of 27.32 ± 25.53 months, ranging from 2.07 months to 176.43 months. Eighty-one patients [male/female (M/F), 55/26; mean age, 28.87 ± 26.15 months] were identified as having acute CALs. The remaining 135 patients (M/F, 77/58; mean age, 26.39 ± 25.20 months) had no CALs. These patients with acute CALs were further divided into two groups: with chronic CALs ($n = 26$; M/F, 19/7; mean age, 36.9 ± 35.9 months) and without chronic CALs ($n = 55$; M/F, 36/19; mean age, 25.1 ± 19.3 months). None had ruptured or occluded CALs. Baseline patient demographics are summarized in Table 1.

Age, sex, and doses of IVIG treatment in KD children with and without CALs

The proportion of older patients (>60 months) in KD children with acute CALs was higher than that of those without acute CALs. The proportion of male patients in KD children

Table 1 Comparisons of demographic and clinical data in KD patients with/without acute CALs and with/without chronic CALs

Factor/ category	KD ($n = 216$)				KD with acute CALs ($n = 81$)			
	Without acute CALs ($n = 135$)	With acute CALs ($n = 81$)	COR (95% CI)	p[a]	Without chronic CALs ($n = 55$)	With chronic CALs ($n = 26$)	COR (95% CI)	p[a]
Age (months)	26.4 ± 25.2	28.9 ± 26.1			25.1 ± 19.3	36.9 ± 35.9		
≤12	43 (31.9)	25 (30.9)	1.00		15 (27.3)	10 (38.5)	1.00	
12–60	80 (59.3)	42 (51.9)	0.90 (0.49–1.68)	0.746	34 (61.8))	8 (30.8)	0.35 (0.12–1.07)	0.066
>60	12 (8.9)	14 (17.3)	2.01 (0.80–5.01)	0.136	6 (10.9)	8 (30.8)	2.00 (0.53–7.54)	0.306
Sex								
Female	58 (43.0)	26 (32.1)	1.00		19 (34.5)	7 (26.9)	1.00	
Male	77 (57.0)	55 (67.9)	1.59 (0.89–2.84)	0.114	36 (65.5)	19 (73.1)	1.43 (0.51–4.01)	0.494
Doses of IVIG treatment								
None	27 (20.0)	14 (17.3)	1.00		6 (10.9)	8 (30.8)	1.00	
1	102 (75.6)	54 (66.7)	1.02 (0.50–2.11)	0.955	42 (76.4)	12 (46.2)	0.21 (0.06–0.74)	0.015
2	6 (4.4)	13 (16.0)	4.18 (1.31–13.37)	0.016	7 (12.7)	6 (23.1)	0.64 (0.14–2.94)	0.569

CALs = coronary artery lesions; CI = confidence interval; COR = crude odds ratio; IVIG = intravenous immunoglobulin; KD = Kawasaki disease.
Data are presented as mean ± standard deviation or n (%).
[a] p Value is estimated by logistic regression.

with CALs was greater than that of those without CALs. However, there were no significant differences between the two groups in terms of age and sex. Compared with KD children without acute CALs, those with acute CALs received more second doses of IVIG treatment ($p = 0.016$). During follow-up of KD children with acute CALs, there were significant differences between KD children with and without chronic CALs in terms of first dose of IVIG treatment ($p = 0.015$) (Table 1).

Laboratory findings in KD children with and without CALs

There were no significant differences between KD children with and without acute CALs in terms of WBC count; band count; hemoglobin level; platelet count; and serum levels of AST, ALT, or CRP. In acute stage, there were significant differences between the two groups in terms of neutrophil count (<54%) ($p = 0.030$). During follow-up of KD children with acute CALs, there were no significant differences between KD children with and without chronic CALs in terms of WBC count; neutrophil count; lymphocyte count; hemoglobin level; platelet count; and serum levels of AST, ALT, or CRP, except for band count (≥3%) ($p = 0.011$) (Table 2).

Multivariate analysis of demographic and clinical data for KD patients with/without acute CALs

The factors remaining significantly associated with acute CALs after multivariate analysis are shown in Table 3. Age and sex were not significantly associated with the presence of acute CALs. The second dose of IVIG treatment was significantly associated with increasing odds of acute CALs [odds ratio (OR) = 5.01, $p = 0.009$]. The neutrophil count (<54%) and platelet count (≤400,000/mm^3) were significantly associated with decreasing odds of acute CALs (OR = 0.44, $p = 0.041$ and OR = 0.42, $p = 0.006$ respectively).

Multivariate analysis of demographic and clinical data for KD patients with/without chronic CALs

The factors remaining significantly associated with acute CALs after multivariate analysis are shown in Table 4. Sex was not significantly associated with the presence of chronic CALs. Age (12–60 months) and first dose of IVIG treatment were significantly associated with decreasing odds of chronic CALs (OR = 0.25, $p = 0.042$ and OR = 0.12, $p = 0.005$ respectively). The band count (≥3%) was significantly associated with increasing odds of chronic CALs (OR = 3.51, $p = 0.032$).

Discussion

Our study demonstrated that neutrophil count, second dose of IVIG treatment, and platelet count were correlated with the risk of acute CALs; on the other hand, age, first dose of IVIG treatment, and band count were correlated with the risk of chronic CALs. Most previous studies have not classified CALs into acute and chronic stage and might not delineate the factors for long-term sequelae of CALs [7–10]. In this series, the distinction of CALs into acute and chronic stage is important for the exploration of IVIG resistance on subsequent remodeling of CALs. Our results suggest that IVIG-resistant patients might be considered for more aggressive therapy, such as additional steroids or infliximab, to prevent CALs in chronic stage [15,16].

Table 2 Distribution and odds ratios for KD patients with/without acute CALs and with/without chronic CALs

Factor/ category	KD ($n = 216$)				KD with acute CALs ($n = 81$)			
	Without acute CALs ($n = 135$)	With acute CALs ($n = 81$)	COR (95% CI)	p[a]	Without chronic CALs ($n = 55$)	With chronic CALs ($n = 26$)	COR (95% CI)	p[a]
	n (%)	*n* (%)			*n* (%)	*n* (%)		
White blood cell count ($\times 10^3/mm^3$)								
>15.5	33 (24.4)	28 (34.6)	1.00		19 (34.5)	9 (34.6)	1.00	
5.5–15.5	96 (71.1)	53 (65.4)	0.61 (0.34–1.12)	0.111	36 (65.4)	17 (65.4)	1.00 (0.37–2.66)	0.995
<5.5	6 (4.4)	0 (0.0)			0 (0.0)	0 (0.0)		
Hemoglobin (g/dL)								
<11.5	81 (60.0)	55 (67.9)	1.00		35 (63.6)	20 (76.9)	1.00	
11.5–15.5	54 (40.0)	24 (29.6)	0.71 (0.40–1.27)	0.245	19 (34.5)	5 (19.2)	0.53 (0.18–1.52)	0.236
>15.5	0 (0.0)	2 (2.5)			1 (1.8)	1 (3.8)		
Polymorphonuclear neutrophil (%)								
>62	46 (34.1)	38 (46.9)	1.00		28 (50.9)	10 (38.5)	1.00	
54–62	42 (31.1)	25 (30.9)	0.72 (0.37–1.39)	0.327	14 (25.5)	11 (42.3)	2.20 (0.76–6.41)	0.149
<54	47 (34.8)	18 (22.2)	0.46 (0.23–0.93)	0.030	13 (23.6)	5 (19.2)	1.08 (0.31–3.79)	0.908
Lymphocyte (%)								
<25	48 (35.6)	35 (43.2)	1.00		24 (43.6)	11 (42.3)	1.00	
25–33	37 (27.4)	26 (32.1)	0.96 (0.50–1.87)	0.913	18 (32.7)	8 (30.8)	0.97 (0.32–2.90)	0.956
>33	50 (37.0)	20 (24.7)	0.55 (0.28–1.08)	0.082	13 (23.6)	7 (26.9)	1.18 (0.37–3.76)	0.786
Band (%)								
<3	75 (55.6)	39 (48.1)	1.00		32 (58.2)	7 (26.9)	1.00	
3–5	33 (24.4)	23 (28.4)	1.35 (0.78–2.34)	0.292	11 (20.0)	12 (46.2)	3.78 (1.36–10.46)	0.011
>5	27 (20.0)	19 (23.5)			12 (21.8)	7 (26.9)		
Platelet count ($\times 1000/mm^3$)								
>400	49 (36.3)	42 (51.9)	1.00		26 (47.3)	16 (61.5)	1.00	
150–400	85 (63.0)	36 (44.4)	0.53 (0.30–0.93)	0.026	27 (49.1)	9 (34.6)	0.56 (0.22–1.45)	0.233
<150	1 (0.7)	3 (3.7)			2 (3.6)	1 (3.8)		
Aspartate aminotransferase (U/L)								
>55	54 (40.0)	31 (38.3)	1.00		22 (40.0)	9 (34.6)	1.00	
15–55	78 (57.8)	45 (55.6)	1.08 (0.61–1.89)	0.801	30 (54.5)	15 (57.7)	1.26 (0.48–3.33)	0.642
<15	3 (2.2)	5 (6.2)			3 (5.5)	2 (7.7)		
Alanine aminotransferase (U/L)								
>45	71 (52.6)	44 (54.3)	1.00		29 (52.70	15 (57.7)	1.00	
5–45	62 (45.9)	33 (40.7)	0.93 (0.54–1.62)	0.805	24 (43.6)	9 (34.6)	0.82 (0.32–2.10)	0.676
<5	2 (1.5)	4 (4.9)			2 (3.60	2 (3.6)		
C-reactive protein (mg/dL)								
≥0.6	118 (87.4)	74 (91.4)	1.00		51 (92.7)	23 (88.5)	1.00	
<0.6	17 (12.6)	7 (8.6)	0.66 (0.26–1.66)	0.374	4 (7.30	3 (11.5)	1.66 (0.34–8.04)	0.527

CALs = coronary artery lesions; CI = confidence interval; COR = crude odds ratio; KD = Kawasaki disease.
[a] p Value is estimated by logistic regression.

Neutrophil activation state and apoptosis have been suggested to play a role in KD pathogenesis [17]. An influx of neutrophils is found in the early stage (7–9 days after KD onset), with a rapid transition to large mononuclear cells in concert with lymphocytes and immunoglobulin A plasma cells [18,19]. Destruction of the internal elastic lamina and, eventually, fibroblastic proliferation occur at this stage, resulting in the formation and development of arteritis in KD. Beiser et al [8] developed an instrument to predict the development of CALs among KD patients. They constructed a sequential risk classification instrument based on easily measured baseline laboratory test results and temperature, including neutrophil count, and no patient classified as at low risk developed CALs [8]. Our finding may be considered to support their report. Band count ≥20% in KD has been considered to be a risk factor for IVIG resistance and CALs [20]; however, in this series, the band count (≥3%) was associated with the risk of chronic CALs. The following reasons may explain the discrepancy in percent bands between Tremoulet et al's [20] study and ours. First, 38.3% of patients with KD in Tremoulet et al's [20] study were IVIG resistant, whereas in ours, 12.2% were IVIG resistant.

Table 3 Multivariate analysis of demographic and clinical data for KD patients with/without acute CALs

Factor/category	KD ($n = 216$)			
	Without acute CALs ($n = 135$)	With acute CALs ($n = 81$)	OR (95% CI)	p[a]
	n (%)	*n* (%)		
Age (mo)				
≤12	43 (31.9)	25 (30.9)	1.00	
12—60	80 (59.3)	42 (51.9)	0.86 (0.43—1.69)	0.652
>60	12 (8.9)	14 (17.3)	1.77 (0.61—5.17)	0.297
Sex				
Female	58 (43.0)	26 (32.1)	1.00	
Male	77 (57.0)	55 (67.9)	1.49 (0.81—2.75)	0.205
Doses of IVIG				
None	27 (20.0)	14 (17.3)	1.00	
1	102 (75.6)	54 (66.7)	1.16 (0.54—2.49)	0.707
2	6 (4.4)	13 (16.0)	5.01 (1.49—16.83)	0.009
Polymorphonuclear neutrophil (%)				
>62	46 (34.1)	38 (46.9)	1.00	
54—62	42 (31.1)	25 (30.9)	0.88 (0.43—1.81)	0.734
<54	47 (34.8)	18 (22.2)	0.44 (0.20—0.97)	0.041
Platelet count ($\times 1000/mm^3$)				
>400	49 (36.3)	42 (51.9)	1.00	
150—400	85 (63.0)	36 (44.4)	0.42 (0.23—0.77)	0.006
<150	1 (0.7)	3 (3.7)		

CALs = coronary artery lesions; CI = confidence interval; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; OR = odds ratio.
[a] p Value is estimated by logistic regression.

Second, the patients in Tremoulet et al's study were ethnically diverse, whereas in ours, they were all Taiwanese [20]. The mechanism of a higher percentage of band count in KD remains unclear and merits additional investigation.

Administration of a single high dose of IVIG (2 g/kg) for 10—12 hours is the standard treatment in KD [5]. However, 7.8—38.3% of KD patients are unresponsive to the initial IVIG treatment [20—25]. In this series, we demonstrated

Table 4 Multivariate analysis of demographic and clinical data for KD patients with/without chronic CALs

Factor/category	KD with acute CALs ($n = 81$)			
	Without chronic CALs ($n = 55$)	With chronic CALs ($n = 26$)	OR (95% CI)	p[a]
	n (%)	*n* (%)		
Age (mo)				
≤12	15 (27.3)	10 (38.5)	1.00	
12—60	34 (61.8)	8 (30.8)	0.24 (0.07—0.91)	0.036
>60	6 (10.9)	8 (30.8)	1.17 (0.25—5.42)	0.840
Sex				
Female	19 (34.5)	7 (26.9)	1.00	
Male	36 (65.5)	19 (73.1)	1.71 (0.48—6.12)	0.411
Doses of IVIG treatment				
None	6 (10.9)	8 (30.8)	1.00	
1	42 (76.4)	12 (46.2)	0.15 (0.03—0.63)	0.010
2	7 (12.7)	6 (23.1)	0.33 (0.06—1.97)	0.226
Band (%)				
<3	32 (58.2)	7 (26.9)	1.00	
3—5	11 (20.0)	12 (46.2)	3.51 (1.12—11.03)	0.032
>5	12 (21.8)	7 (26.9)		

CALs = coronary artery lesions; CI = confidence interval; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; OR, odds ratio.
[a] p Value is estimated by logistic regression.

that the IVIG-resistant patients are at a higher risk for acute and chronic CALs, as was observed in previous reports [22—24]. The mechanism of IVIG in reducing inflammation of KD is not clearly understood. Some scoring systems, including age; illness duration; platelet count; ESR; and concentrations of hemoglobin, CRP, lactate dehydrogenase, and alanine aminotransferase, had been used as predictors of IVIG resistance [10,20,24—26]. The predictive value of these scoring systems, especially the Egami score system in different ethic groups, is still not widely accepted [24,26]. Further studies are needed to elucidate the mechanism of IVIG for identifying new targets for therapy in IVIG-resistant patients.

Muta et al [9] reported that older children with KD experience a delay in both diagnosis and treatment with IVIG, and, in children older than 6 years, age is an independent risk factor for cardiovascular sequelae in KD. Age less than 1 year is also a risk factor [7,13]. These younger patients often present with incomplete clinical features, adding difficulty in making accurate diagnosis and offering timely treatment. Our analysis of the risk factor of age in chronic KD is compatible with these previous reports [7,9,13].

Other predictors of poor coronary outcome in KD patients in previous studies included low hemoglobin level, low albumin level, high WBC count, high CRP level, and male sex [7,8,10—12]. Platelet count has been identified as a marker for increased risk of CALs, but controversy remains regarding whether decreased or increased platelet count is the high-risk factor [7,10—12]. In this series, high platelet count ($>400{,}000/mm^3$) was significantly associated with high risk of acute CALs. In contrast to the aforementioned studies, Honkanen et al [13] found that the degree of anemia, platelet count, ESR, and WBC count were not predictive of CALs.

Several limitations in this study need to be specified. This study was a single-center retrospective cohort investigation without a large number of patients. In addition, these traditional clinical and laboratory markers for development of CALs need to be evaluated jointly with novel biomarkers in future studies. In this study, the use of Japanese Ministry of Health criteria might underestimate the true incidence of CALs in patients with KD. We could not rule out the influence of the different brands of IVIG used to treat patients on outcome. A multicenter cohort study is therefore suggested for the future.

In conclusion, the results of this study suggest that the effects of neutrophil count, doses of IVIG treatment, and platelet count on CALs in acute KD are important. Age, doses of IVIG treatment, and band count are related to the persistence of CALs in the chronic stage of KD.

Acknowledgments

This research was supported in part by the Kaohsiung Veterans General Hospital (VGHKS99-082, VGHKS100-086) and Zuoying Armed Forces Hospital (9910).

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