

Clinical Presentation and Cardiovascular Outcome in Complete *versus* Incomplete Kawasaki Disease

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Objective: To compare the demographic, clinical, and laboratory features of incomplete and complete presentations of Kawasaki disease. **Methods:** A retrospective review of the electronic case records between January 2000 and December 2015 in a tertiary care referral center of Sohar, Oman. **Results:** 31 out of 64 children (48.4%) had incomplete presentation. Children with incomplete presentation had higher incidence of skin rash, lymphadenopathy and conjunctivitis. They took a longer time to show clinical response to intravenous immunoglobulin [mean (SD) 52.6 (17.4) h vs 40.1 (16.4) h, $P=0.005$], and had prolonged hospitalization [mean (SD) 6.2 (2.5) d vs 4.6 (1.7) d, $P=0.009$]. **Conclusion:** Children with incomplete presentation of Kawasaki disease tend to have prolonged hospitalization but short- and long-term coronary outcomes appear to be similar.

Keywords: Coronary aneurysm, Mucocutaneous lymph node syndrome, Outcome, Vasculitis.

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Kawasaki disease (KD) is an idiopathic self-limited systemic vasculitis of childhood originally reported from Japan, and is increasingly being recognized worldwide [1]. Diagnosis of KD is essentially clinical and incomplete/atypical presentations pose diagnostic challenges for the clinician due to lack of specific diagnostic tests [2]. Approximately 15-20% of patients with KD are known to have incomplete presentation, and the incidence over the years is thought to be rising [3-5].

The aim of our study was to characterize the clinical presentation and long-term outcome of incomplete KD in children admitted to a tertiary-care referral center and compare it with those who presented with complete form of KD.

METHODS

The study was conducted at Regional Teaching Hospital, Sohar in the North Batinah region of the Sultanate of Oman with the approval of the Ethics committee of Director General of Health Services, Ministry of Health. From the hospital electronic database (Al-Shifa-3 plus), we retrieved records of children with KD as primary diagnosis between January 2000 and December 2015 using International Classification of Diseases version 10.

The diagnosis of KD was made when a child of any age-group presented with unexplained fever ($>38^{\circ}\text{C}$) for

at least five days and four of the following: (i) bilateral conjunctival congestion without exudate, (ii) changes of the oral mucous membrane (any 1): congested pharynx, congested/fissured lips, strawberry tongue, (iii) polymorphous rash, (iv) changes of the extremities: desquamation or edema, and (v) unilateral lymphadenopathy. When the patients did not fulfill four of the above criteria and other diagnoses could be reasonably excluded, incomplete KD was diagnosed if the patient had symptoms that associate frequently with KD with raised inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and >3 supplemental laboratory criteria that included echocardiographic features [3]. Baseline laboratory work-up included hemoglobin, white cell counts, and inflammatory markers like CRP and/or ESR and trans-thoracic echocardiography. Additional tests like urine microscopy, urine/blood culture, abdominal ultrasonography, renal and liver function test were done based on clinical circumstances and the discretion of the treating physician.

Upon diagnosis, all patients received intravenous immunoglobulin (IVIG) (2 g/kg) infused over 10-12 hours and oral aspirin (80 mg/kg/d). IVIG resistance was defined as persistent or recrudescing fever 48 hours after the completion of immunoglobulin infusion. Echocardiology was performed by an in-house physician

TABLE I CLINICAL AND LABORATORY CHARACTERISTICS OF CHILDREN WITH COMPLETE AND INCOMPLETE KAWASAKI DISEASE

Clinical/laboratory finding	Complete Kawasaki (n=33)	Incomplete Kawasaki (n=31)	P value
Conjunctivitis; n (%)	29 (87.8)	10 (32.2)	0.004
Skin rash; n (%)	27 (81.8)	10 (32.2)	0.001
Extremity changes; n (%)	19 (57.5)	20 (64.5)	0.616
Lymphadenopathy; n (%)	25 (75.7)	12 (38.7)	0.004
Strawberry tongue; n (%)	11 (33.3)	04 (12.9)	0.077
Respiratory symptoms; n (%)	10 (30.3)	01 (0.03)	0.006
Hemoglobin (g/dL)*	10.4 (1.22)	10.1 (0.88)	0.389
Platelet count*	495.3 (230)	486 (130)	0.155
White cell count (x10 ⁹ /L)*	14.4 (4.4)	13.6 (4.1)	0.195
Neutrophils%*	67.9 (13.8)	61.13 (18.4)	0.149
Serum sodium (mEq/L)*	133.6 (2.1)	133.4 (2.8)	0.085
Alanine transaminase (U/L)#	14.5 (11-23)	33.5 (14-157)	0.034
Serum creatinine (μmol/L)#	31 (30-37)	26 (19-30)	0.082

*Mean (SD); #Median (IQR).

trained in pediatric echocardiography. Japanese guideline was used to assess coronary aneurysms [6].

The groups were compared using chi-square test or Fisher exact tests for categorical variables. Non-parametric tests were used for continuous variables whenever appropriate. Statistical tests were 2-tailed with a significance level of P<0.05. Data were analyzed using SPSS software version 16.

RESULTS

Sixty-four children were diagnosed with KD during the study period, and 31 (48.4%) out of them had incomplete presentation. No cases of recurrence, and one instance involving siblings were noted. Median (IQR) age at presentation in incomplete KD group was 25 (14,48) months, and was comparable to that in KD, 26.5 (14,81) months. Children with incomplete KD had greater male preponderance (2.6:1) than those with complete presentation (1.3:1). Pattern of seasonal variation was similar in both groups was less marked in incomplete KD group. Presenting clinical features and important laboratory findings in two groups are compared in **Table I**. Specific infections identified at the time of diagnosis included rotavirus diarrhea, streptococcal pharyngitis (1 case each) and culture-positive urinary tract infection (5 cases).

Table II shows that children in incomplete KD group took a longer time to show clinical response to IVIG infusion, mostly in the form of resolution of fever. Those with incomplete presentation had a significantly longer duration of hospital stay (mean difference 1.6 d)

(**Table II**). Similar rates of IVIG resistance was observed in both groups.

Thirty children (47%) showed echocardiographic abnormalities in acute stage: 8 had early coronary artery dilation, 7 had perivascular brightness without aneurysm, and 5 each showed evidence of myocarditis, pericardial effusion and valvular insufficiency. Three children developed late coronary artery aneurysms. There were no significant differences between the groups in terms of cardiovascular involvement.

DISCUSSION

Our data revealed a high proportion of incomplete KD in a single-center cohort. Children with incomplete KD were less likely to manifest lymphadenopathy, skin rash and non-exudative conjunctivitis. Our comparison did not reveal any age-group specific differences in the prevalence of incomplete KD. Delayed response to IVIG

TABLE II MANAGEMENT TIMELINE AND INCIDENCE OF IVIG RESISTANCE IN KAWASAKI DISEASE

Characteristic	Kawasaki Disease	
	Complete	Incomplete
Fever duration (d)*	6.1 (3.6)	7.5 (4.8)
Time to diagnosis (d)#	6 (6-8)	8 (6.5-10)
Hospital stay (d)*‡	4.6 (1.7)	6.2 (2.5)
Response to IVIG (h)*‡	40.1 (16.4)	52.6 (17.4)

*Mean (SD); #Median (IQR). Five cases in complete group and two cases in incomplete group had IVIG resistance. IVIG- intravenous immunoglobulin; ‡P <0.01.

WHAT THIS STUDY ADDS?

- Compared to classic presentation, children with incomplete presentation tend to have longer hospital stay with similar cardiovascular outcomes.

in incomplete KD group in our study could be a reflection of disease severity or due to delayed diagnosis. This observation has not been reported previously. Our finding of prolonged hospital stay in incomplete KD despite adequate treatment negates the possibility of lack of treatment leading to differences in duration of hospital stay reported earlier [7]. Delay in clinical response contributed to prolonged hospitalization.

The proportion of incomplete KD in our study is higher compared to other recent studies conducted outside Japan [7-10]. Relatively larger proportions have been reported from India (41%) and Spain (40%) [11,12]. Acute and late coronary outcomes in two groups were similar in our cohort which is in agreement with previous observations [4,6]. However, several investigators have observed a higher risk of coronary artery aneurysms (CAA) in incomplete KD [9,13,14]. A Greek study reported reduced risk of CAA [8]. A recent meta-analysis suggested marginally increased risk of CAA in incomplete KD (OR=1.44; 95% CI 1.1,1.8), particularly in infants and among Asians [15].

Our analysis is limited by the inherent drawbacks of the retrospective study design. Lack of related information such as CSF findings, d-dimer, serum IgE, and cardiac troponin could have led to missing of some cases. Echocardiography was performed by more than one observer and body surface area-adjusted coronary artery z-scores were unavailable.

Incomplete KD, reportedly missed before the publication of 2004 American Heart Association guidelines, probably continues to be missed and/or underreported. Future studies need to focus on epidemiological and clinical characterization, and also address the uncertainties in prognostication.

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