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Kawasaki Disease: Review of 5 years

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Received: July 18, 2017; **Published:** August 18, 2017

Abstract

Objective: To describe the clinical characteristics and management of Kawasaki disease in Centro Hospitalar Conde de São Januário in Macau.

Methods: We retrospectively reviewed the electronic medical records of patients with KD who were admitted to our hospital between 1/1/2011 and 31/12/2015. We compared patients with complete KD to the atypical KD. Overall treatment was also analysis.

Results: We identified 44 patients with a mean age of 26.6 months. The male-to-female ratio was 1.9. Infants constituted the largest group of patients. Among these, 28 had complete KD and 16 atypical KD. The group with complete KD had significantly higher rates of change in the extremities, exanthema, mucositis, lymphadenopathy; and a significantly lower rate of coronary artery dilatation (46% vs 87% in the incomplete KD group). Laboratory tests were not significant different from each group. We use IVIG on day 6.5 ± 1.3 day of fever starts. 26/44 obtained cardiac complication. Although 3/44 had poor response to first dose of IVIG, all of them resolved after 2nd treatment.

Conclusion: KD cases in our hospital compatible with cases from other study, including clinical presentation, laboratory test and % of cardiac lesion involved. IVIG+ aspirin remained the first line therapy in acute phase, but there are also IVIG resistance occupying ~10% of cases, mainly managed by 2nd dose IVIG. Most of the cardiac complication resolved after appropriate treatment. Although management for medication is well documented, follow-up plan still needs further study, especially in those without coronary lesion.

Keywords: *Kawasaki Disease; Lymphadenopathy; IVIG*

Introduction

It has been 50 years since Dr. Tomisaku Kawasaki first described the syndrome of Kawasaki disease (KD). It is also known as mucocutaneous lymph node syndrome, occupied most prominent cause of acquired coronary artery disease in childhood [1]. Diagnosis is, however, still based on clinical signs and symptoms. The Japanese Kawasaki Disease Research Committee and the American Heart Association already published guideline and flowchart about them [2]. Treatment of acute disease with immunoglobulin (IVIg) and high-dose aspirin can reduce the risk of developing coronary artery abnormalities. On the other hand, patients may suffer from long-term morbidity as a result of coronary arteries scarring, which may further result atherosclerosis [3].

Kawasaki disease is the most leading cause of acquired heart disease in children in developed countries [4]. The incidence of KD varies in different parts of the world although it is most common in Asia. A retrospective study of the incidence of KD in Beijing from 1995 to 1999 ranged from 18.2 to 30.6 per 100 000 children below 5 years old [5]. More than 20 years ago, there were 5 to 7 cases of KD each year between 1991 - 1997 in Centro Hospitalar Conde de São Januário, Macau (CHCSJ) [8]. There was no updated information and this study aimed at report the characteristics of KD in our hospital.

Methods

Patients diagnosed with KD between Jan 2011 to Dec 2015 were identified from the hospital computer systems. Data gathering were completed based on information available in the CHCSJ electronic medical records. This study summarizes the data analysis stated above.

There is no confirmatory diagnostic test for KD. We based on the American Heart Association (AHA) published diagnostic criteria for complete and atypical KD [6]. The criteria are similar to those of the Japanese Circulation Society, including fever for at least 5 day and fulfilling at least 4 of the following:

1. Changes of the oral cavity and lips: cracked and erythematous lips, strawberry tongue
2. Polymorphous rash: maculopapular, erythema multiform-like or scarlatiniform rash, involving extremities, trunk and perineal regions
3. Bilateral conjunctivitis, nonpurulent
4. Changes in the extremities (erythema of the hands and feet, desqumation of the hands and toes in weeks 2 and 3)
5. Cervical lymphadenopathy (> 1.5 cm in diameter).

Patients who do not meet this would be diagnosed with atypical KD if presented with coronary dilatation, or with ≧ 3 laboratory findings according to the evaluation of incomplete (atypical) Kawasaki disease [10].

Other population datas including sex and age were obtained from the CHCSJ medical systems. The statistic analysis relied on student's t test and the chi-square test to compare the two groups. P values smaller than 0.05 were considered significant.

Results

During these 5 years, a total of 44 cases of KD were diagnosed. There were 29 (65.9%) boys and 15 (34.1%) girls. Male to female ratio is 1.9:1. The age range was 2 months old to 81 months old. The mean age at disease onset is 26.6 months. There are 2 peaks of age prevalence. Infants formed the largest group and at around age of 5 years (60 months) formed another peaks (Figure 1). The December got the highest incidence while the September got the lowest. Exanthem, conjunctival conjestion and mucositis were present in over 80% of cases meanwhile cervical lymphadenopathy was not so common (62%). Above all, 16 (36.3%) belongs to atypical KD, all of them are below 2 years old or over 4.5 years old (Table 1).

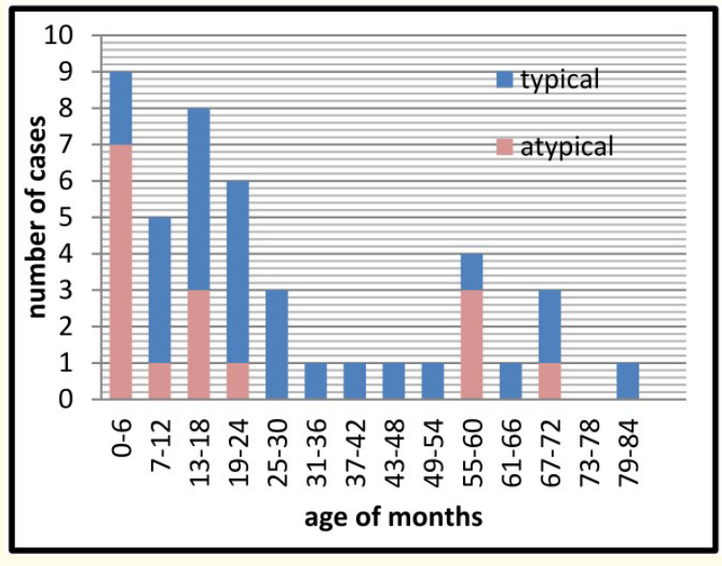

Figure 1: *Typical KD and atypical KD distribution in CHCSJ, 2011 - 2015.*

Principal criteria	No. of patients	%
Changes in the extremities	24	54.5 %
exanthem	36	81.8 %
Conjunctival conjection	38	86.4 %
mucositis	35	79.5 %
Lymphadenopathy	27	61.4 %

Table 1: *Proportion of principal criteria feature of patients with KD.*

For the CBC part of laboratory test, Hemoglobin(Hb) were the only significantly difference between complete KD and atypical KD. Anemia was found in 93% of patients overall, usually with normal values for corpuscular volume, indicating inflammatory related anemia. The leukocyte count at admission was 15.26 ± 4.1 x 10^9/L in complete KD and 16,4 ± 4.8 x 10^9/L in atypical KD (p = 0.2). Platelet count was normal at admission but increase subsequently to about 600,000 X 109/L (day 9 after admission). Some study showed low platelet is risk for coronary artery lesion [10]. High values were noted at admission for both CRP and ESR, without further significant compared to later (day 7 after admission). As for the biochemistry, serum sodium levels were at lower limit in both groups. Liver enzyme elevation is common feature in KD. Among our patients, 32% had pyuria (Table 2).

		All (mean ± SD)	Complete KD (mean ± SD)	Atypical KD (mean ± SD)	*P* value
Hb on admission	(g/dl)	10.99 ± 0.94	11.36 ± 0.88	10.36 ± 0.69	<0.0001
WBC on admission	(10^9 /L)	15.70 ± 4.36	15.26 ± 4.13	16.43 ± 4.77	0.2
PLT on admission	(10^9 /L)	350 ± 116	344 ± 113	359 ± 123	0.34
Platelet on day 3	(10^9 /L)	368 ± 103	359 ± 123	364 ± 100	0.38
max platelet	(10^9 /L)	605 ± 207	576 ± 199	646 ± 198	0.17
ESR on day 2	(mm)	68.6 ± 36	77 ± 25.9	69 ± 42.4	0.29
max ESR	(mm)	65 ± 37	68.4 ± 41.9	58.1 ± 29.2	0.22
CRP	(mg/dl)	9.17 ± 5.0	8.6 ± 5.4	10.1 ± 4.2	0.17
Sodium	(mmol/l)	135.7 ± 2.2	135.6 ± 2.5	135.7 ± 1.5	0.35
AST	(IU/L)	80.5 ± 81.5	83.6 ± 77.9	74.9 ± 89.7	0.37
ALT	(IU/L)	90 ± 120	116.4 ± 134.0	66.5 ± 84	0.07
GGT	(IU/L)	110.2 ± 108.9	114.5 ± 117.9	86.5 ± 44.5	0.37
Urine leukocyte esterase positive (%)	%	34.1	39.3	25.0	0.33

Table 2: *The blood and urine analysis of KD cases. Hb: Hemoglobin; PLT: Platelet; max: The Peak Data During the Whole Disease Course; Platelet on day 3: Platelet Count on Day 3 of Admission.*

Coronary artery dilatation is significantly more common in the group with atypical KD (87% vs 46%, P = 0.007). On the other hand, Pericardial effusion (21% vs 18%)and MR/TR (46% vs 37%) is not significantly different (Figure 2).

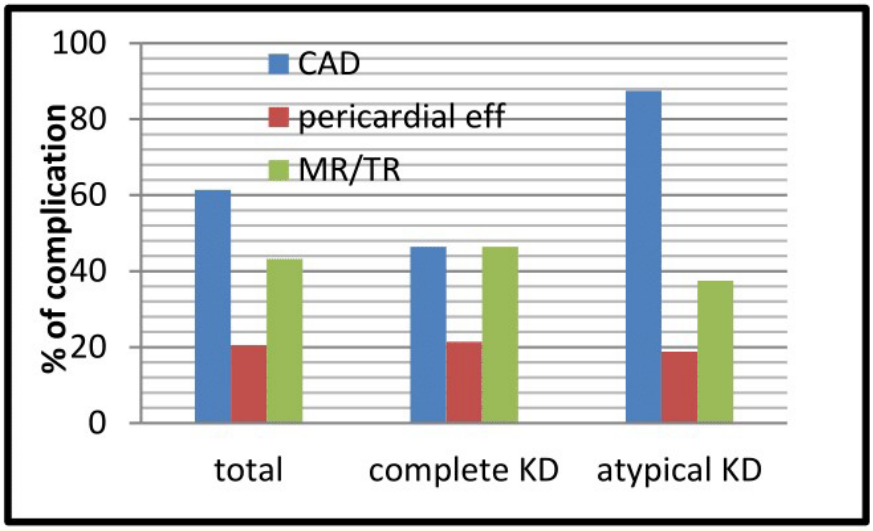

Figure 2: *Cardiac involvement of KD. CAD: Coronary Artery Dilatation; eff: Effusion; MR/TR: Mitral Regurgiatation/Tricuspid Regurgitation.*

An underlying active infection was suggested during the course of the disease in 9/44 patients, 5 in complete KD and 4 in atypical KD. It did not have significantly increased risk of coronary artery dilatation (P = 0.89) (Figure 3).

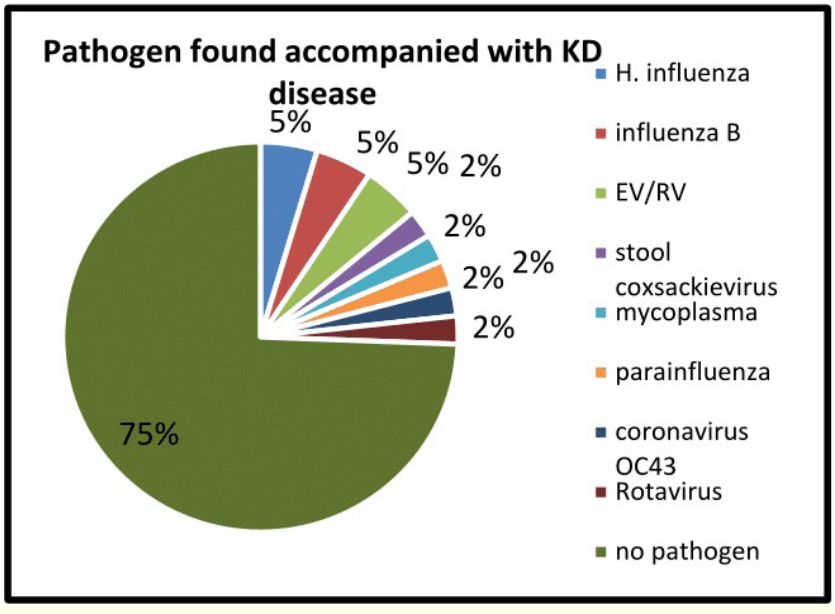

Figure 3: *Pathogen found accompanied with KD disease. EV/RV: Enterovirous/Rhinovirus.*

Intravenous gamma-globulin and aspirin were prescribed to all children in this study. Averagely, the treatment started on day 6.5 ± 1.3 days of fever. For those without cardiac complication, 78% stopped aspirin before 8 weeks of treatment. No significant difference in complete KD and atypical group ($p > 0.05$). 3/44 (6.8%) had poor response to 1st IVIG, aged 3 months, 7 months and 29 months respectively. All with marked elevated CRP(> 13 mg/dl) and ALT (> 200 U/L). After 2nd dose IVIG, all fever resolved. Among 26/44 (59.1%) with coronary artery dilatation, all of which resolved of coronary disease during follow up.

Discussion

This study is focus on CHCSJ retrospectively collected datas of KD. It included all cases recorded within 2011 - 2015 in CHCSJ. However, we do not count the cases in the other hospitals or private clinics in Macau. The case number of KD in Macau would be higher. DU ZD., *et al*. reported that KD incidence of 18.2 to 30.6 per 100,000 for children younger than 5 years in Beijing, while in Taiwan, similar study report incidence of 54.9 per 100,000 children younger than 5 years. These suggest that the incidence of KD in Chinese population is less then that of Japanese and higher than in Caucasians [5,7].

In our study, coronary artery dilatation was significantly more in the group of atypical KD (87% vs 46%, $P = 0.007$). In the past, more echocardiography performed in atypical KD to support the diagnosis before IVIg, leading to recruitment bias. The overall rate of CAD in previous study of all KD cases in our hospital is 41% (1991 - 1997) [8]. Contradicting studies reported incomplete presentation of Kawasaki disease in children to be associated with higher risk, similar risk, or lower risk of coronary artery abnormalities compared to children with complete presentation [9].

There is no specific diagnostic test for KD, but some laboratory findings are characteristic. During the acute stage of KD, leukocytosis is typical. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) are always elevated in the acute phase of the disease. Although platelet count elevated in the disease course, the initial platelet count was usually not high. Some study showed low platelet is risk for coronary lesion [10]. Moderate elevated liver enzyme is common in KD. A literature about biopsy of KD patient showed evidence of hepatic bile duct involvement with necrosis of bile duct epithelium [8]. In our study, GGT was elevated 13/14 (93%) in those with this item checked. However, there was no significant difference between the KD and atypical KD groups regarding the liver enzyme. Some clinical manifestations which are not lists above should suggest KD, including irritability, and erythema at the site of prior BCG vaccination [11]. URTI symptom or GI upset was noted at admission in 57% cases. There are 38% KD patients with respiratory symptom and 20% with GI symptoms. Not data about arthralgia is recorded. We are unable to collect data on these features through our computer system since it is not always marked in the admission notes. On the other hand, our patients showed some laboratory evidence of KD. 34% of patients involved had urine leukoesterase positive, which is similar to previous report (13 - 45%) [12]. Transuretral catheterization may help in differentiating between tubulointerstitial nephritis and urethral inflammation. Some suggested that pyuria was more often seen in KD than adenoviral infection [13]. Hyponatremia was noted in 12 (27.2%) of 44 patients with KD in our study, in keeping with previous study (27 - 44%), which may indicate inappropriate antidiuretic hormone secretion caused by cerebral vasculitis, nephritis or dehydration [14]. Of those under 3 months of age, all CSF in the routine fever work up showed elevated protein level, without pleocytosis. This may explain why patients with KD had some extent of irritability.

Day of fever when admission is 4 ± 1.8 days. IVIG was used on day 6.5 ± 1.3 day of fever starts. All patient received IVIG in our study. In Dr. Marques., *et al*. previously study in our hospital, 91% KD were treated with IVIG (1991 - 1997). During follow up, 78% of the cases stopped aspirin before 8wk (no difference in KD and atypical group, $p = 0.053$). 26/44 with cardiac complication. Even treated with high dose IVIG, 5% develop transient coronary artery dilation [15]. 3/44 (6.8%) had poor response to first dose of IVIG. All of them are with elevated ALT (> 80 U/L) and marked elevated CRP (> 10 mg/dl). One of them had platelet count < 300 x 109/L. Using scoring system, all of them had Egami score ≥ 3 points, while only one got Kobayashi score ≥ 5 pointes. Although further research is necessary, it seems advisable to adapt this scoring system for risk-stratified strategy so as to raise alert to possible resistance cases and avoid risk of developing CAD [16]. All of our cases resolved after 2nd IVIG treatment.

All the KD patients are arranged to follow up in pediatric cardiologist and echocardiogram. There is still no evidence of atherosclerosis risk among patients with normal coronary arteries in childhood. Further large cohorts of middle-aged patients with past history of KD should be analyzed.

Conclusions

KD characters in CHCSJ are consistent with cases from other studies, including clinical presentation, laboratory test and rate of cardiac lesion involved. IVIG plus aspirin remained the first line therapy in acute phase, but there are also IVIG resistance occupying ~10% of cases, mainly managed by 2nd dose IVIG. Most of the cardiac complications resolved after appropriate treatment. Although management for medication is well documented, long term follow-up still needs further study, especially in those without coronary lesion.

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Volume 5 Issue 2 August 2017