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A TEN YEAR REVIEW OF KAWASAKI DISEASE THE CHINESE GENERAL HOSPITAL EXPERIENCE

Doris Chua, M.D.*
Marissa Cueto-Velasco, M.D.
Eleanor Galvez, M.D.

ABSTRACT

Kawasaki disease presents with unusual features involving respiratory, gastrointestinal, urinary, cutaneous, skeletal and neurologic systems. This paper aims to describe the profile of Kawasaki disease patients in CGHMC. A total of 28 patients with Kawasaki disease from April 1988 to April 1999 were reviewed and analyzed using descriptive statistics from 3 months to 9 years with peak incidence among the less than 1 year old. Male to female ratio of 1.15 : 1. Polymorphous rash, conjunctival injection and cervical lymphadenopathy were the most common manifestations. Atypical presentations which failed to meet the criteria set by the Center for Disease Control were noted in 21% of the study population. Hemolysis and vasomotor reactions were also observed in 2 patients given IVIG. All 28 patients received aspirin. Of the 22 patients given IVIG, all except one received high dose IVIG (2g/kg). Six patients had cardiac involvement despite IVIG administration within the recommended period. No significant difference in sociodemographic and clinical parameters were noted between patients with and without cardiac involvement. Thus a sound basis as to which patients would benefit from IVIG and the timing of its administration needs to be established. A study with adequate sample size requiring the use of 2-D echo is critical to document cardiac involvement among suspected cases of Kawasaki disease. An analytical type of research is necessary to determine the risk factors of Kawasaki disease in the future. A meta-analysis of hospital data can be done on a nationwide basis.

Kawasaki Disease was first described by Tomisaku Kawasaki in 1967 as an "acute febrile mucocutaneous lymph node syndrome." In the United States, it was first described by Melish et al in 1974[1] and in the continental US by John et al in 1976.[2] Since then, there were reported outbreaks of Kawasaki disease in New England in 1980-1992.[4] In Australia, there was also report of 139 from May 1993 – June 1995.[5] It now appears to have a worldwide distribution.

In the Philippines, the first case of Kawasaki disease was reported by Mabilangan in 1982 [6] and another 2 cases by Songco in the same year.[7] Two more cases were reported by Santos Ocampo in 1983[8] and three cases from the Visayas in 1984.[9] The first adolescent case was reported by Victorio in 1986.[10] The first documented coronary aneurysm was reported in a 5 year old boy with Kawasaki disease by Arciaga in 1987.[11]

There were also a number of case series locally. A four year review of 40 patients was done by Pecache at the Hospital of the Infant Jesus from 1990 – 1993.[7] While Santiago did a six year review in Children's Medical Center risk included 18 patients, four of which had coronary artery aneurysm.[12]

The increasing incidence of Kawasaki disease worldwide and in the local setting was also noted in Chinese General Hospital and Medical Center (CGHMC) when we reviewed our records from 1988 to the present: 1988 – 1 case; 1990 (1); 1993 (2); 1994 (1); 1995 (3); 1996 (5); 1997 (2); 1998 (8); 1999 (5).

Kawasaki disease with atypical presentation has been observed more frequently in the recent past. Burns reported a series of 8 patients younger than 6 months of age with atypical presentation which were associated with high morbidity and mortality.[13] Avner described a 5 year old girl who fulfilled only three of the diagnostic criteria (fever, conjuctivitis, adenopathy) and developed giant coronary aneurysm.[14] In this review, we also observed a number of atypical Kawasaki disease cases who did not fulfill the criteria set by the American Heart Association and yet developed cardiac involvement.

A nationwide survey (1995) in Japan among 8958 Kawasaki disease cases given intravenous immunoglobulin (IVIG) revealed that the proportion of those with cardiac sequelae was higher in patients with IVIG than those without IVIG regardless of age and sex. Their explanation for this phenomenon is that those who were more severely affected were more likely to be treated with IVIG.[15] On the other hand, Pecache observed that the proportion of patients who developed coronary aneurysm was the same (25%) for those who received aspirin alone (7/28) and for those who received aspirin and IVIG (4/12).[7]

Keywords. Kawasaki disease, descriptive profile
*Active Consultant, Department of Pediatrics, Chinese General Hospital Medical Center

Based on these findings, there seems to be a need to review the criteria in the diagnosis and protocol of managing Kawasaki disease. With the increasing number of cases with atypical presentation reported abroad and in the Philippines, early recognition and treatment is vital. The authors were encouraged to present their present experience at Chinese General Hospital and Medical Center hoping that the study will contribute to the existing body of knowledge on Kawasaki disease in the midst of scarcity of local data.

OBJECTIVES

The study was undertaken to describe the profile of Kawasaki cases at CGHMC as to the sociodemographic background and clinical presentation; to compare the cases of Kawasaki disease patients with or without cardiac involvement according to demographic variables (sex and age), duration of fever, laboratory findings, type of treatment and timing of IVIG administration; to determine the adverse reactions to IVIG and describe the Kawasaki cases with typical presentation but with unusual features and Kawasaki cases with atypical presentation.

MATERIALS AND METHODS

The medical records of children admitted at Chinese General Hospital diagnosed as Kawasaki Disease from April 1988-April 1999 were reviewed. The criteria for diagnosis of Kawasaki disease is based on clinical findings as set by the Centers for Disease Control Atlanta GA.[15]

Diagnostic Criteria for Kawasaki Disease

1. Fever of 5 or more days associated with at least 4 of the following changes:

   a. Bilateral conjunctival injection
   b. One or more changes of the mucuos membranes of the upper respiratory tract including pharyngeal injection, injected lips, dry, fissured lips and "strawberry tongue".
   c. One or more changes of the extremities including peripheral erythema
   d. Rash, polymorphous, primarily truncal
   e. Cervical lymphadenopathy

2. The illness cannot be explained by some other known disease process

Demographic, clinical, laboratory, echocardiographic, therapeutic, and follow-up data were extracted from each medical record. Typical Kawasaki disease was diagnosed by the presence of fever of 5 or more days with at least 4 or 5 criteria or fever plus 3 major criteria if coronary artery aneurysm was recorded by echocardiography.

Fever was defined as equal to or more than 37.8°C. The day of illness was counted from the onset of fever. The first post-treatment days was defined as the 24-hour period beginning with the initiation of aspirin plus IVIG therapy. By echocardiography, a coronary artery was considered abnormal if the diameter of the internal lumen was at least 3 mm or if the internal diameter of a segment was at least one and a-half times that of an adjacent segment or if the lumen was clearly irregular. Patient whose echocardiography showed an internal coronary diameter greater than 8 mm was considered to have giant coronary artery aneurysm.[17]

ESR was determined by Wintrobe method. CBC and other laboratory tests were performed by standard methods in the clinical laboratory. Chest X-ray, ECG and or 2-D echocardiography were done either on admission or on follow-up after discharge.

This study is retrospective and descriptive in design. For analysis, descriptive statistics were used including the measures of central tendency and measures of dispersion. Ratio and proportion were also calculated for the frquency distribution of each variables. Appropriate tables and graphs were constructed.

RESULTS

Twenty eight patients were diagnosed to have Kawasaki Disease at Chinese General Hospital and Medical Center during the study period. Ages ranged from 3 months to 9 years (Fig.1). Kawasaki disease occurred most among the 0-12 months with 8 cases. However, up to 3 years (25-36 months), the incidence is still high. Figure shows the sex distribution with 54% of the cases being males and the rest were females with a ratio of 1.15:1 As to ethnicity, 54% were Filipinos, 25% Filipinos-Chinese, 14% Chinese and 7% Japanese-Filipinos (Fig.3).

Fig.1

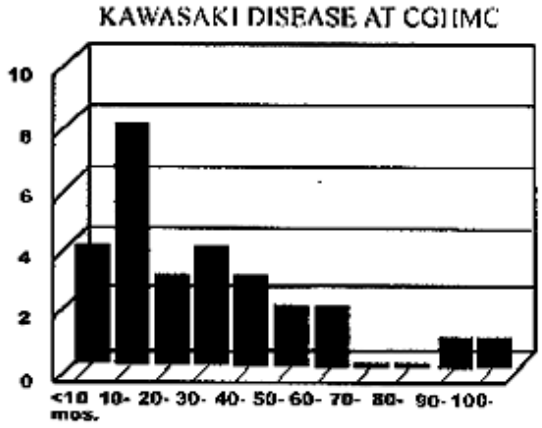
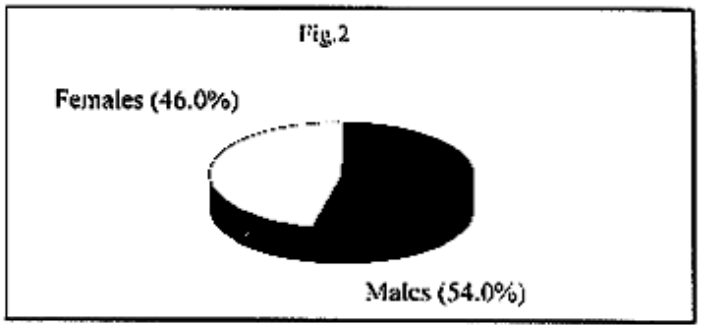
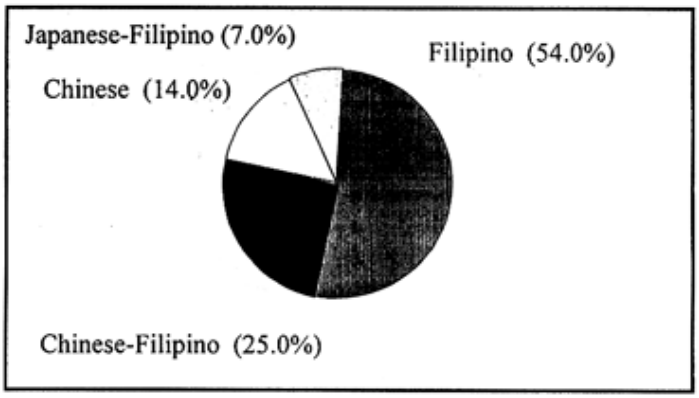


Fig.2



DISTRIBUTION OF KAWASAKI CASES BY RACE AT CGHMC

Fig. 3



DISTRIBUTION OF KAWASAKI CASES BY RACE AT CGHMC

Table 1 shows the major features manifested by our patients. Fever of more than 5 days were noted in all our patients. The fever ranged from 5-14 days with a mean duration of 9 days. Polymorphous rash (89.2%), conjunctival injection (78.6%) and cervical lymphadenopathy (67.8%) were the most common principal manifestations in our patients. The size of some cervical lymph nodes were not measured. The other manifestations commonly observed were changes in the extremities (peripheral edema and erythema 53.6%); periungual desquamation 17.8%; strawberry tongue 32% and mucosal erythema 25%.

TABLE 1. PERCENTAGE DISTRIBUTION BY MAJOR FEATURES OF KD* AT CGHMC

Major Features	No. of Cases	Percentage
Fever	28	100.00
Injected conjuctivae	22	78.50
Mucuos membrane changes		
Strawberry tongue	9	32.10
Mucosal erythema	7	25.00
Red fissured lips	22	78.60
Cervical lymphadenopathy	19	67.80
Changes in extremeties		
Peripheral erythema	15	53.60
Peripheral edema	15	53.60
Periungal desquamation	5	17.80
Rash	25	89.20

N=28
*KD = Kawasaki disease

The unusual and associated features of Kawasaki disease are summarized in Table 2. The most common respiratory findings were cough and colds. A case with pulmonary edema with ascites and hydrocoele was observed.

The associated features of the gastrointestinal tract included anorexia (35.7%), vomiting and diarrhea (25%), abdominal pain (10.7%), abdominal distention (10.7%), ileus (7.1%) and hydrops of the gallbladder (7.1%). Hepatomegaly, melena, bilious vomiting and ascites were seen in another case.

Proteinuria was the most common finding in the urinary tract (52%). Other findings included pyuria (26%), hematuria (12%) and hydrocoele (3.6%). Pyuria is defined as more than 5 leucocytes per high power field. Urine culture and sensitivity was done on only one patient and this did not show significant results.

Perianal rash was noted in 28% of patients between 3-17 days of illness (mean = 9 days). The onset of periungual desquamation appeared between the 4-21th day of illness (mean = 13 days).

Arthritis and arthralgia were seen in 7.15% of patients. Irritability was the most common neurologic manifestation (64.9%) in our study.

TABLE2. PERCENTAGE DISTRIBUTION BY UNUSUAL & ASSOCIATED FEATURES OF KD* AT CGHMC

Unusual and Associated Features	No. of cases	Percentage
Respiratory		
Cough	7	25.00
Colds	8	28.70
Pulmonary edema	1	3.60
Gastrointestinal		
Anorexia	10	35.70
Vomiting**	7	25.00
Diarrhea	7	25.00
Abdominal pain	3	10.70
Abdominal distention	1	3.60
Ileus	2	7.10
Hepatomegaly	1	3.60
Hydrops of the gall bladder	2	10.70
Melena	1	3.60
Ascites	1	3.60
Urinary		
Pyuria^	6	6.00
Proteinuria^	12	52.00
Hematuria^	3	12.00
Hydrocele	1	3.60
Cutaneous		
Perineal rash	7	25.00
Skeletal		
Arthralgia/Arthritis	2	7.10
Neurologic		
Irritability	18	64.90

N=28
*KD = Kawasaki
**1 with bilious vomiting
^ 5 without urinalysis

All of the 28 patients received aspirin at a dose of 80-100 mg/kg/day which was decreased to 3-10 mg/kg/day once the fever subsided. Twenty two patients were given IVIG, all of whom received a single high dose (2g/kg) except for one who received the low dose (400 mg/kg/day)for 5 days.

Based on literature, the risk factors for coronary involvement in patients with Kawasaki disease are below 1 year of age, male, sex, prolonged duration of fever (>14days), elevated platelet count and ESR level. [16,18]

A comparison of our cases in CGHMC with and with out cardiac complication, according to these risk factors is seen in Table 3 and 4. Among the 15 patients who did not develop cardiac complications, 47% were below 1 year old. There were more males than females. Platelet count was elevated in 47% of patients. This determination among patients with normal platelet however was done prior to the tenth day of illness when the rise

was not yet expected. As for the ESR level, all patients had elevated results. Unfortunately, data was available only for 8 patients.

Only a small percentage (13%) of those without cardiac complications had fever of 14 days duration (mean = 9 days, range of 5-14 days). Three of the 15 cases did not receive IVIG. Among those given IVIG (12), one received a low dose. The timing of giving IVIG was mostly within the recommended day with only 4 patients receiving IVIG after the tenth day.

A total of 5 patients developed cardiac abnormalities (Table 4), of these 20% were below 1 year and 60% were predominantly male. Forty percent had an elevated platelet (>450,000) taken before day 10. According to Literature, the platelet count is expected to increase after this period. The ESR were all elevated. The IVIG were given within the recommended day (</=10th day of illness) except for one who received the IVIG on day 13. The mean duration of fever was 10 days.

Based on the data presented, the findings for patients with or without cardiac complications described according to the risk factors above are almost the same. (Table 5).

ADVERSE REACTIONS TO IVIG

Among the 22 patients who received IVIG, 2 patients developed adverse reactions during infusion. These reactions consisted of hemolysis in one patient, while another patient developed vasomotor reactions.

Hemolytic reaction was observed in a 5 2/12 male of Filipino-Japanese ancestry with a weight of 25 kgs. He was treated with a single 2 gm/kg/dose IVIG within 12 hours and Aspirin at 100 mg/kg/day. Eleven days after giving IVIG, the patient complained of tenderness and submandibular mass on the left side of the neck, 3x3 cm, smooth, fluctuant and movable. He was also noted to have pallor and epigastric tenderness. The rest of the physical examination was normal.

The laboratory results showed CBC with hemoglobin of 7 gms, hematocrit .21 with a WBC of 41,700, ESR of 73 mm/hr. Reticulocyte count was 0.482. Urine was dark yellow, hazy with RBC 0-2/hpf, WBC 1-3/hpf and trace albumin. Serum amylase was 109 U/L, LDH: 469 U/L, Serum sodium: 4.3 mmol/L, BUN: 5.7 mmol/L, Creatinine: 65 mmol/L. Stool was negative for occult blood.

TABLE 3. KD* PATIENTS WITHOUT CARDIAC INVOLVEMENT WITH SELECTED RISK FACTORS^

Case no. n=15	Age	Sex	Plate x 100 (Day Taken)	ESR mm/hr (Day Taken)	Fever duration Days	Dose of IVIG Type of Rx (given day)
1	8 mos.	M	250 (D8)	53 (D9)	8	
2	29 mos.	F	220 (D2)	/	5	400mg (D6)
5	42 mos.	M	450 (D8)	57 (D11)	12	2g (D11)
8	10 mos.	F	287 (D7)	37 (D9)	7	2g (D23)
9	93 mos.	F	529 (D9)	/	7	2g (D10)
12	15 mos.	M	526 (D21)	31 (D22)	14	2g (D8)
15	56 mos.	M	Adeq**(D9)	57 (D9)	11	2g (D8)
16	10 mos.	F	260 (D4)	/	7	2g (D8)
19	9 mos.	M	377 (D8)	/	12	/
20	11 mos.	F	314 (D9)	54 (D9)	12	2g (D10)
21	30 mos.	M	282 (D14)	55 (D5)	6	2g (D6)
22	13 mos.	F	599 (D15)	/	14	2g (D16)
24	3 mos.	M	654 (D6)	/	6	2g (D7)
25	62 mos.	M	539 (D12)	73 (D27)	13	2g (D7)
28	3 mos.	F	543 (D6)	/	6	/
	mean =26.2 mos		8M: 7F 1.14:1		mean = 9	

*KD = Kawasaki disease
^Normal 2-D Echo
** Adeq = Adequate

Worthwhile noting from table 4 were that three patients with cardiac complications received IVIG within the recommended period (tenth day). Therefore giving IVIG earlier would be more beneficial. Yanagawa suggested that IVIG treatment is effective if administered on and before the seventh day of illness.[15]

Osmotic fragility test showed initial hemolysis with 0.50% NaCl, complete hemolysis with 0.44% NaCl (Control:initial hemolysis with 0.48% NaCl, complete hemolysis 0.42% NaCl). G6PD assay was negative. Abdominal ultrasound showed minimal ascites, thickened gall baldder wall, non dilated ducts, no liver, pancreatic, splenic or renal pathology.

TABLE 4. KD* PATIENTS WITH CARDIAC INVOLVEMENT WITH SELECTED RISK FACTORS

Case No.	Age	Sex	Platelet Count In thousands day taken	ESR mm/hr (day taken)	Day IVGG given	Fever duration in days	Cardiac Complication (Day 2-D Echo was taken)
6	48 mos	M	446 (D8)	56 (D8)	9	9	Giant aneursym LCA**,RCA^7-8 mm (D23)
13	46 mos	M	293 (D7)	55 (D7)	8	7	Borderline LCA 2.2-2.9 mm (D34); Normal after 1 year
14	22 mos	F	374 (D7)	61 (D7)	10	10	Mild pericardial effusion
18	11 mos	M	653 (D9)	54 (D12)	13	1	LCA 2.4 mm (D9); Normal (D26) Mild pericardial effusion
27	60 mos	F	525 (D12)	59 (D9)	9	10	RCA 4 mm, LCA 3.7 mm (D13); Normal (D30)

*KD = Kawasaki disease
**LCA = Left coronary artery
^RCA = Right coronary artery

Peripheral smear showed microcytic hypochromic RBC with slight poikilocytosis, no abnormal WBC seen, few reactive lymphocytes, increased platelets. Gastroenterology consult was done. The patient was placed on H-2 blocker (ranitidine IV) and antacids. He was also seen by a hematologist. The assessment was hemolytic reaction based on the presence of reticulocytosis, dark-colored urine, anemia and some spherocytes. Packed red cells were transfused. The patient was asymptomatic after transfusion. Repeat CBC upon discharge showed hemoglobin of 12 gm, hematocrit .38, WBC 14,500, neutrophils (0.62), lymphocytes (0.25), monocytes (0.3), eosinophils (0.08), basophils (0.02), platelet count 755,000. On follow-up, the patient was asymptomatic.

Vasomotor reaction was experienced by a 6 year old Filipino – Chinese male with a weight of 17.7 kgs. He complained of dyspnea, chest tightness and wheezing, skipped beats and pulmonary edema a day after IVIG (2 g/kg given in 16 hours) administration. The total fluids including the volume of IVIG was computed at the maintenance rate for his age. There was no fluid overload. Initial chest X-ray showed cardiomegaly with normal pulmonary vascular marking. Repeat chest X-ray done 24 hours after IVIG showed cardiomegaly with questionable pulmonary edema. The patient had skipped beats, ascites and hydrocoele.

BUN was 4.5 mmol/L, creatinine 0.41 mmol/L, Sodium 140 mmol/L, Potassium 4.3 mmol/L, Chloride 103 mmol/L. Flat plate of the abdomen showed no pathology. Symptoms were relieved by slowing down the rate of IVIG infusion. Salbutamol inhalation and diuretics (Furosemide IV) at 0.6 mg/kg was given. The patient was discharged. He, however developed a giant coronary aneursym.

KAWASAKI DISEASE WITH UNUSUAL FEATURES

Two typical Kawasaki disease cases but with unusual presentations were seen in our study. The findings of pulmonary edema, ascites and hydrocoele were demonstrated in case no.6. A four year old male who developed pulmonary edema and cardiomegaly (documented by chest X-ray), carditis, skipped beats (sinus pause on ECG), ascites and hydrocoele. Two-D echocardiogram done on Day 23, showed a giant aneurysm, right, and left coronary arteries measuring 7-8 mm. Repeat 2-D echo on the 57th day of illness showed the left coronary artery to be persistently dilated (5-8 mm) with mild pericardial effusion. A grade 1/6 holosystolic murmur at the apex, 4th intercostal space, left midclavicular line was noted at 5 ½ months of illness. Two – dimensional echocardiogram showed hypokinesia from middle to base of the posterior and inferior wall of the left ventricle. The patient was scheduled for cardiac catherization but was lost to follow-up.

Another patient (case no.27) had associated gastrointestinal features of hepatomegaly, vomiting, ascites and melena. She was a 5 year old female who presented with fever, throat pain, 5 episodes of bilious vomiting, melena, abdominal distention, ileus and hepatomegaly prior to the appearance of the major features of Kawasaki disease. Prothrombin time was 11.8 seconds (control: 11.2 seconds, INR=1.0). Prothrombin ratio =1, activity = 84.6%, APTT was 43.2 seconds (control: 33.9 seconds).

CBC on admission showed leucocytosis (23,000). Neutrophils (0.83), lymphocytes (.07), basophils (.09), Monocytes

TABLE 5. SUMMARY OF CARDIAC FINDINGS INKD*ACCORDING TO RISK FACTORS^

Risk Factors	Without Cardiac Involvement n=15	With Cardiac Involvement n=5
1. Age<1 year	47%	20%
2. Sex (male)		
number	8/15	3/5
ratio	1.14:1	1.5:1
3. ESR >20mm/hr	100%	100%
4. Platelet >450,000	47%	40%
5. Duration of Fever	13%	40%
>/=14 days	mean =9days	mean =10 days

*KD = Kawasaki disease
\Criteria set by Beiser & Gersony

(0.1), Hemoglobin (101 gm/dl), Hematocrit (.30), Platelet Count (323,000). Repeat CBC showed WBC 13,600, neutrophils (.77), lymphocytes (.09), bands (.08), monocytes (.04), platelet count (442,000), hemoglobin (.81) and hematocrit (.24). No reticulocytosis. SGPT was 63 U.L. Stool was positive for occult blood. Meckel's diverticulum study using technetium 99-pertechnetate was negative for ectopic gastric mucosa. Ultrasound of the whole abdomen showed hepatomegaly, non-dilated ducts, non-specific minimal cul de sac fluid, no gallbladder, pancreatic, splenic or renal pathology were noted. The patient was given vitamin K, H2 blocker, IV fluids and packed red cells transfusion. High dose IVIG (2gm/kg) was given on the 9th day of illness. Aspirin was started when melena ceased and was advised to complete intake for 6 months. 2-D echocardiogram done on the 28th day of illness showed borderline size right coronary artery aneurysm. Presently she is asymptomatic. She is scheduled for repeat echocardiography after a year.

DISCUSSION

The lack of a definitive laboratory test for Kawasaki disease limits the clinician's ability to diagnose this disease entity with speed and accuracy. The clinician has relied on the well-described features of Kawasaki disease to assist in the diagnosis. The age distribution, male predominance and characteristics of the principal symptoms of our patients were similar to those reported in the US, Japan, Australia and Thailand. [1,4,19,20] Most cases were seen in children younger than 3 years of age. A Review of literature showed that the disease is rare after 8 years. This was true in our setting with only one of our patient being 9 years old.

The most common feature was the rash seen in 89.2% of our patients followed by injected conjuctivae 78.6%, cervical lymphadenopathy 67.8% and irritability 64.3%. These findings were similar with that of Pecache.[7] Reports from Japan and the US showed that cervical lymphadenopathy was the least frequent diagnostic feature seen.[21] However, in this study it was one of the most common feature seen as in the study of Pecache. Could this be due to a concomitant Primary Koch's infection as supported by chest X-ray findings in some patients? Unfortunately PPD was not done for any of our patients.

Intravenous immunoglobulin preparations can contain aggregates with anticomplementary activity.[21,22] These preparations can produce vasomotor symptoms including chills, nausea, flushing, chest tightness and wheezing. The formation of immunoglobulin aggregates can be substantially reduced by using stabilizing agents, such as maltose, in the immunoglobulin preparation. Infusion over several hours also reduces the likelihood of vasomotor symptoms. Today, all intravenous immunoglobulin preparations in the US are manufactured with stabilizing agents, are acidified and are recommended for infusion over several hours.

Leucocytosis with shift to the left was seen in 86% of the patients. Marked thrombocytosis was not observed since the blood samples were taken before the 10th day of illness whereas the expected rise is seen in the second and third week after the onset of fever.[22]

Renal involvement such as urethritis, priapism, epididymo-orchitis, cystitis, prostatitis, acute renal failure, interstitial nephritis, nephrotic syndrome and isolated azotemia were reported in the literature.[26] These were not seen in this study. Only one patient had hydrocoele. Urinalysis of our patients showed proteinuria (52%), pyuria (26%) and microscopic hematuria (12%).

Gastrointestinal symptoms like diarrhea and vomiting are common and mild in Kawasaki disease except in the presence of hydrops of the gall bladder. The most common symptoms of hydrops of the gall bladder was abdominal pain, occasional vomiting and abdominal distention. Gall bladder distention was best detected by ultrasonography. This is thought to be due to extension of periportal inflammation to the cystic duct and is generally

self-limited.[21] The patients were placed under close monitoring and medical management. No surgical intervention was done. Symptoms resolved spontaneously. One of the patients with hydrops of the gall bladder with concomitant melena developed coronary aneurysm. Could it be possible that patients with more severe gastrointestinal symptoms was more prone to develop coronary aneurysm?

Perineal or perianal rash and/or desquamation was a common cutaneous manifestation in a study done in Taiwan.[23] Seventy five percent of the patients had this manifestation whereas it was seen infrequently in other parts of the world. It begins in 3 or 4 days as erythematous macules or papules in the perianal area that rapidly progresses to confluence. Within 5-7 days of onset of illness, the rash will desquamate.[24,25] It always precedes fingertip and toe desquamation by 2-6 days. The reason for the appearance of this rash in the groin is not clear. However, the increased trauma, heat and moisture affecting the area may play a role. The presence of this rash may facilitate early diagnosis of Kawasaki disease and hence may influence the initiation of early therapy.[24]

In this study, 28.6% of patients developed perineal rash. On the average, the rash appeared in 9 days (range 3-17 days). Periungual desquamation was also noted in 28.6% of patients. The average day of desquamation is 13 days (range 4-21 days). While the appearance of the perineal rash may help in the early diagnosis of Kawasaki disease, we cannot rely on this since it may appear late or not at all, as in our study.

Respiratory tract symptoms such as cough, rhinorrhea and abnormal chest X-ray are common.[23] These were also observed in our study. The findings observed were bronchopneumonia, perihilar pneumonitis and Primary Koch's infection.

Neurologic manifestations were relatively uncommon in our study with similar findings in previous reports from Japan by Huang in the US and Japan.[21]

No significant difference between the Kawasaki disease patients with and without cardiac complications with regard to age, male sex, elevated ESR, thrombocytosis, duration of fever in the study maybe due to the limited sample size and timing of laboratory determination. High dose IVIG is effective in reducing the incidence of coronary aneurysm, if this is administered within 10 days from the onset of illness. [17,23] All patients (21) except one were given high dose IVIG. However, despite giving IVIG as early as the 8th day of illness, there were some who developed coronary abnormalities. Many reports have suggested that IVIG treatment is effective if administration is started on or before day 7 of illness.[15] The high percentage of patients with cardiac sequelae in those treated with IVIG was possibly due to the fact that these were the more severe cases of Kawasaki disease. A baseline 2-D echo is ideal to document if coronary lesions are already present prior to IVIG therapy. If there are fianancial constraint, baseline EKG and chest X-ray should be taken. If the EKG and chest X-ray showed abnormalities, a baseline 2-D echo should then be requested.

Marasini claimed that late administration of IVIG appears to have some benefit in his study.[17] Those given IVIG later than 10 days showed resolution of the coronary aneurysm. This was also observed in some patients despite late administration of IVIG.

TABLE 6. ATYPICAL CASES OF KAWASAKI DISEASE AT CGHMC

Case no.	*Age	Sex	Criteria Fulfilled	Platelet Count In thousands (day)	ESR mm/hr (day)	IVGG (day)	Fever duration	2-D Echo Findings (day)
1	8 mos	F	3-cervical lymphadenopathy rash peripheral erythema	250 (D8)	53 (D9)	none	8 days	Normal (D29)
5	42 mos	M	3-conjuctival injection pharyngeal injection and red lips	450 (D8)	57 (D11)	2g (D11)	12 days	Normal (D26)
8	10 mos	F	3-red lips -peripheral edema and perirgual rash	287 (D7)	37 (D7)	2g (D7)	7 days	Normal (D8) Normal (D81) Normal (D165)
18	11 mos	M	2-conjunctival red lips	653 (D9)	54 (D12)	2g(D13)	14 days	Mild pericardial effusion, RCA** mm, LCA^3.7 mm (D13) Normal (D30)
22	18 mos	F	3-pharyngeal red lips rash cervical lymphadenopathy	599 (D15)	none	2g(D16)	14 days	Normal (D14) Normal (D45)
28	3 mos	F	3-conjunctival injection rash peringual desquamation	543 (D6)	none	none	6 days	Normal (D34)

*mean + 15 mos
**RCA = right coronary artery
^LCA = left coronary artery

ADVERSE REACTIONS TO IVIG

The use of IVIG has been associated with remarkably few side effects. Minor adverse reactions include fever, chills, nausea, abdominal pain, flushing, headache, dizziness and joint pain. Severe reactions have been found occassionally. Most side effects are aborted or prevented by decreasing the rate of infusion or by pretreatment with aspirin, diphenhydramine or both.[26]

Hemolytic reactions and thrombosis are rarely reported as a consequence of IVIG administration. It maybe due to high dose IVIG administered in patients with IgA deficiency. Comenzo et al reported a patient who developed significant hemolysis because of the quantity of anti-A1 antibody present.[22] The ability of the anti-A1 antibody to cause clinically significant hemolysis maybe attributed to the dose of IVIG given; the titer of the anti-A1 antibody in the IVIG preparation, the strenght of the patient's A1 antigen expression or a combination of all these factors.[27]

Intravenous immunoglobulin preparations can contain aggregates with anticomplementary activity.[26,27] These preparations can produce vasomotor symptoms including chills, nausea, flushing, chest tightness and wheezing. The formation of immunoglobulin aggregates can be substantially reduced by using stabilizing agents such as maltose, in the immunoglobulin preparation. Infusion over several hours also reduces the likelihood of vasomotor symptoms. Today, all intravenous immunoglobulin preparations in the US are manufactured with stabilizing agents, are acidified and are recommended for infusion over several hours.

The vasomotor reactions and failure of IVIG to prevent coronary aneurysm in this patient maybe due to the presence of aggregates with anticomplementary activity in the particular IVIG preparation given this patient. It is also possible that there is IgA deficiency in this patient.[28] Unfortunately, no IgA level was obtained in both of these patients who developed adverse reactions.

Physicians using IVIG should be aware of the range of adverse reactions associated with passive transfer of blood type antibodies so that they may diagnose such reactions promptly, implement appropriate transfusion recommendations and modify therapy as needed.

Experts in North America consider a child with fever having 2 of the 5 criteria and with coronary arteritis by 2-D echocardiography to have atypical Kawasaki disease. In Japan, a child with any 3 of 5 criteria (with or without coronary arteritis) is considered to have atypical Kawasaki.[21]

Roughly 20% of our cases presented atypically, i.e. having fulfilled less than 4 of 5. Among the six patients who had atypical presentations, one patient had only 2 diagnostic features and still developed cardiac involvement. The diagnosis of Kawasaki disease in infants is often difficult because they do not have the classic signs and symptoms and individual manifestations may be subtle. Coronary aneursym were thought to occur predominantly in the subacute phase of Kawasaki disease in young children with severe disease and prolonged fever.

Not only are fewer clinical findings necessary for one to suspect Kawasaki disease but also the individual criteria are subject to wide variation.[29] The maximum level of platelet count and ESR and duration of fever are of value only in retrospect.[30] Hence, baseline 2-D echo is highly recommended especially in atypical cases. Clinicians must be aware of the wide variation of clinical presentation of Kawasaki disease so that he can take an aggressive approach in making the diagnosis, in obtaining early cardiac evaluation and prompt initiation of therapy.[11] A need to review our criteria for the diagnosis of Kawasaki disease is vital.

SUMMARY AND CONCLUSION

A 10 year review of Kawasaki cases at Chinese General Hospital and Medical Center showed that the disease is more common in males. Peak age was below 1 year. Polymorphous rash, conjuctival injection and cervical lymphadenopathy were the most common principal manifestations in our patients.

All 28 patients received aspirin. Twenty two patients received high dose IVIG (2g/kg) except for one patient who was given 400 mg/ kg/dose for 5 days. Cardiac abnormalities were noted in 5 patients treated with high dose IVIG. One patient had a giant coronary artery aneurysm, four patients had a cardiac complications consisting of borderline coronary artery aneurysms and mild pericardial effusion. Repeat echocardiography of 3 patients were normal. No significant difference in age, male sex, thrombocytosis, elevated ESR level and duration of fever were noted in those Kawasaki patients with and without cardiac involvement.

Three patients with cardiac involvement received IVIG within the recommended period. This may suggest giving IVIG as early as the seventh day of illness or as soon as the diagnosis is made. It is also possible that these patients who received IVIG had more severe cardiac involvement. A baseline 2-D echo is ideal to document if coronary lesion are already present prior to IVIG administration.

Adverse reactions to IVIG were noted in 2 patients given IVIG which consist of hemolysis and vasomotor reactions. Physicians should be aware of these reactions, so that appropriate measures can be instituted when the situation arise.

Kawasaki disease is also associated with features pertaining to the respiratory, gastrointestinal, urinary, cutaneous, skeletal and neurologic systems.

Twenty percent of our patients who did not fulfill the 4 out of 5 criteria set for Kawasaki disease were labeled as atypical Kawasaki disease. Most of our cases fulfilled only 3 criteria. One patient with 2 criteria fulfilled developed coronary artery aneurysm which eventually resolved. Baseline 2-D echo prior to IVIG therapy and early administration of IVIG is recommended for patients with atypical presentations and unusual features.

RECOMMENDATIONS

1. Do a baseline 2-D echocardiogram in all patients as soon as the diagnosis of Kawasaki disease is made prior to giving IVIG. Regular follow-up is also recommended to monitor the progress of coronary artery aneurysms.
2. As soon as the diagnosis of Kawasaki Disease is confirmed give IVIG before the 7th day of illness since diagnosis is made on clinical criteria. Our findings have shown that four patients developed coronary abnormalities even if IVIG was given within 8-10th day of illness.
3. Platelet count will not be helpful if done in the first week since the expected rise is on the second and third week of illness. However, elevated platelet count is not one of the criteria for diagnosis. The thrombocytosis will be documented if taken on the 2nd and 3rd week of illness.
4. Do a meta-analysis of data from all hospitals in the country in the absence of a nationwide study.
5. Do a prospective study to determine risk factors for Kawasaki Disease and its cardiac sequelae.
6. Always review the criteria for the diagnosis of Kawasaki disease as not to miss the atypical cases.

LIMITATION OF THE STUDY

The limitation of the study include having a small number of cases. We have compiled only 28 cases. The laboratory examinations were not complete in all patients. The timing of laboratory determination is not uniform. Many of the attending physicians did not request for actual platelet count, ESR and 2-D echocardiogram, so some of the data were lacking.

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