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Caguiat PI. Cardiac Involvement in Kawasaki Disease Patients

Pilarica I. Caguiat, MD*
Cherica A. Tee, MD*
Leonila F. Dans, MD*

*Department of Pediatrics, University of the Philippines, College of Medicine-Philippine General Hospital

Correspondence:
plar_12@yahoo.com

Email:

The authors declare that the data presented are original material and have not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all the authors, who have met the requirements for authorship.

ORIGINAL ARTICLE

CARDIAC INVOLVEMENT IN KAWASAKI DISEASE PATIENTS: A RETROSPECTIVE STUDY

ABSTRACT

Background: Kawasaki disease is a self-limited disease but it can lead to potentially fatal cardiac complications if not detected and managed accordingly.

Objective: To determine the incidence of cardiac involvement in patients with Kawasaki disease admitted in PGH

Methods: Medical records of patients with KD admitted from January 2012 to December 2013 were reviewed. Demographic, clinical, laboratory, chest radiographic, electrocardiographic, and echocardiographic data were recorded. The course, management, length of hospital stay, clinical outcome, duration of OPD follow-up, and medications were evaluated.

Results: Thirty-eight patients with mean age of 2.67 ± 2.26 years old, 66% males with KD were included. Fifty-nine percent had cardiac involvement, and among those with cardiac involvement, 68% have coronary artery dilatation. Seventy-six percent of cases received intravenous immunoglobulin (IVIG) with 55% receiving IVIG within 10 days of illness. The initial cardiac findings resolved in the subsequent 2d-echo after IVIG except for some coronary artery abnormalities, which resolved in 5 ± 3.11 months during follow-up. There was no mortality. The possible predictive factors for the development of cardiac abnormalities published in other studies were not found to be significantly associated in this study population.

Conclusion: The incidence of cardiac involvement in patients with Kawasaki disease among children admitted in PGH is 59% with68% having coronary artery dilatation, higher than in other published studies.

KEYWORDS:
Kawasaki disease, coronary artery aneurysm, IVIG

INTRODUCTION

Kawasaki disease (KD) or mucocutaneous lymph node syndrome is an acute febrile vasculitis in childhood first described in 1967 in Japan by Dr. Tomisaku Kawasaki.[1] It is a self-limited disease but may cause cardiac complications such as coronary artery aneurysm in 15 to 25% of patients, which if left untreated, can lead to myocardial infarction, sudden death or ischemic heart disease. Nowadays, it is the leading cause of acquired heart disease in children in the developed countries, surpassing acute rheumatic fever.[2] There is no specific laboratory test available and the diagnosis lies in clinical criteria. However, there are cases which are difficult to recognize such as those with incomplete clinical courses that can cause a delay in the diagnosis and management and thus place the patients at risk of cardiac complications. It is therefore important to recognize KD early to prevent the complications and death.

In our tertiary hospital, there are diagnosed cases of KD, but there is still no published data on the prevalence of KD in the hospital. There is also no review done on the clinical profile of these patients, the incidence of cardiac involvement, management, and the outcome.

The study was undertaken to determine the incidence of cardiac involvement in patients with Kawasaki disease among children admitted to a tertiary hospital. Specifically, this study was done to determine the demographic factors, clinical features, and laboratory findings that are associated with an increase in the odds of cardiac disease among patients with KD; to compare the cases of KD patients with or without cardiac involvement according to demographic variables (sex and age), duration of fever, cardiac findings, diagnostic results, type of treatment and timing of intravenous immunoglobulin; to describe Kawasaki cases with typical presentation but with unusual features and Kawasaki cases with atypical presentation; and to describe the course, management (i.e., treatment with intravenous immunoglobulin, if any, and aspirin), length of hospital stay, clinical outcome, duration of OPD follow-up of each patient.

METHODOLOGY

This retrospective chart review was performed at the Department of Pediatrics of the Philippine General Hospital. Medical records and echocardiogram records of subjects less than 19 years old admitted from January 2012 to December 2013 with the diagnosis of typical and atypical KD as identified from the database of the Sections of Cardiology and Rheumatology were evaluated. The following information was extracted: demographic, clinical, laboratory (complete blood count, ESR and/or C-reactive protein, urinalysis, AST, ALT) chest radiographic, electrocardiographic, and echocardiographic data. The course, management (i.e., treatment with intravenous immunoglobulin, if any, and aspirin), the length of hospital stay as well as the clinical outcome of each patient were recorded. The duration of OPD follow-up of each patient as well as maintenance medications was traced and recorded. The approval of the UP Manila Research Ethics Board was obtained before commencement of the study.

For analysis, the incidence of cardiac involvement was calculated as the number of KD patients with cardiac involvement over the total number of KD patients in a two year period. Results were presented as the mean $\pm$ standard deviation for quantitative variables and number (proportion, 95% CI) for qualitative variables. A multivariate analysis of cardiac involvement of the demographic and clinical features and

laboratory results (fever more than 10 days, male sex, age less than 1 year old, hemoglobin less than 10mg/dl, platelet count >500,000/mm, incomplete KD, Neutrophils >75%) were also performed to determine Odds Ratio with 95% confidence interval for each variable. A p-value less than 0.05 was considered statistically significant.

RESULTS

Thirty-eight patients were diagnosed to have KD at the tertiary hospital during the study period, January 2012 to December 2013. Mean age at diagnosis was 2.67 ± 2.26 years, age range being 2 months to 9 years old. Most of the patients (84%) were less than 5 years of age. There were 25 boys (66%) and 13 girls (34%) giving a male to female ratio of 1.9:1. Eighteen percent of patients had co-morbidities: four patients having bronchial asthma, one patient had G6PD deficiency, one patient had an inguinal hernia and one patient had patent ductus arteriosus. All patients were Filipinos.

Seventy-one percent of the cases presented within 10 days of illness while the remaining (29%) cases presented after 10 days of fever. Mean duration of fever at the time of admission was 9.23 ± 5.17 days. Forty-five percent of patients were initially diagnosed with various diseases such as respiratory tract infections, urinary tract infection, tonsillopharyngitis, or pneumonia before admitted as KD.

Table 2 lists the presenting signs and symptoms of KD patients. Conjunctivitis, oral and extremity changes were present in at least 70% of cases while cervical lymph nodes were less common (45%). Additional clinical features seen consisted of anorexia (39%), cough (47%), colds (24%), irritability (45%), gastrointestinal symptoms including diarrhea (18%), vomiting (18%), and abdominal pain (18%). The cardiovascular examination of patients was normal except for eight patients (21%) who had tachycardia. No patient had gallop rhythm, decreased heart sounds or murmur on auscultation.

Table 1. Demographic and clinical features of children with Kawasaki disease.

Characteristics	Number (Percentage)
Age (n=38)	2.67 ± 2.26 (2mos – 9 years)
Sex (n=38)	
Male	25 (66%)
Female	13 (34%)
Co-morbidities	7 (18%)
Clinical Features (n=38)	
Fever, days (mean) (range)	9.2 ± 5.12 (5– 26)
Rash	24 (63%)
Non-exudative conjunctivitis	28 (74%)
Cervical lymphadenopathy	17 (45%)
Erythema of lips & oral mucosa	32 (84%)
Changes in extremities	29 (76%)
Cough	18 (47%)
Colds	9 (24%)
Anorexia	15 (39%)
Vomiting	7 (18%)
Diarrhea	7 (18%)
Abdominal pain	7 (18%)
Irritability	17 (45%)
Perineal rash	2 (5%)
Cardiac PE (n = 38)	
Tachycardia	8 (20.5%)
Gallop rhythm	0
Decreased heart sounds	0
Murmurs	0

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Table 2. Clinical features of Kawasaki disease patients on presentation.

Characteristics	Number (Percentage)
Fever	38 (100%)
Erythema of lips & oral mucosa	32 (84%)
Changes in extremities Rash	29 (76%)
Non-exudative conjunctivitis	28 (74%)
Rash	24 (63%)
Cervical lymphadenopathy	17 (45%)

Complete blood counts were taken for most of the patients. One patient went home against advice prior to laboratory work-ups were taken. Fifty-three percent (19/36) of patients had anemia for age, 53% had neutrophilic leukocytosis and 50% had thrombocytosis. Twenty patients had erythrocyte sedimentation rate (ESR) taken and out of the 20 patients, 100% have elevated ESR. Twenty-one of the patients had their C-reactive protein (CRP) obtained and 90% had elevated CRP. Fourteen patients had their AST and ALT taken and 14% had elevated AST while 64% had elevated ALT. Twenty patients had a urinalysis and 36% of them had pyuria. Only five patients had their chest radiographs taken and four patients had findings of pneumonia, pneumonitis, bronchitis and hyperaerated lungs and one had no significant chest findings. Only 13 patients had their electrocardiographs taken and seven patients (54%) had sinus tachycardia and without evidence of arrhythmia or ischemia.

An echocardiogram was done in 37 of the patients and 22 (59%) had abnormal findings. One patient, who went home against medical advice, did not have his echocardiogram done. A total of 15 patients (41%) had coronary artery dilatation or a total of 19 patients (51%) with coronary artery abnormalities. The pattern of coronary artery involvement are as follows: left main coronary artery 30% (n=11), left anterior descending artery 22% (n=8), right main coronary artery 27% (n=10), circumflex branch in 11% (n=4) . Four patients (11%) had normal-sized coronary arteries but with irregular borders and six patients (16%) had pericardial effusion. Three patients had mitral regurgitation (8%). No patient had left ventricular dysfunction.

Table 3. Diagnostic findings of patients with Kawasaki disease.

Diagnostic Findings	Values, mean (range)
Laboratory features	
White blood cell count (n=36)	16.43 ± 5.57 (5.55– 28.64)
Neutrophils (n=36)	0.66 ± 0.15 (0.26– 0.9)
Hemoglobin (n=36)	102.3 ± 11.07 (79– 126)
Hematocrit (n=36)	0.31 ± 0.03 (0.24– 0.37)
Platelet count (n=36)Elevated	517 ± 206.05 (177– 1082)
Erythrocyte sedimentation rate (n=20)	
Elevated ESR	
Normal ESR	20 (100%)
Elevated C-Reactive protein (n=21)	0
Elevated CRP	19 (90.4%)
Normal CRP	2 (9.6%)
Elevated Aspartate transaminase (n=14)	2 (14%)
Elevated AST	12 (86%)
Normal AST	
Elevated Alanine transaminase (n=14)	9 (64%)
	5 (3.6%)
Elevated ALT	
Normal ALT	8 (36%)
Pyuria (n=22)	14 (64%)
With pyuria	
Without pyuria	

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Chest Radiographs	
Abnormal findings (n=5)	4 (80%)
Electrocardiogram Findings	
Sinus tachycardia (n=13)	7 (54%)
Arrhythmia(n=13)	0
Myocardial ischemia (n=13)	0

Echocardiograph Findings	
Dilated coronary artery (n=37)	15 (41%)
Left main coronary	11 (30%)
Left anterior descending	8 (22%)
Right main coronary	10 (27%)
Circumflex branch	4 (11%)
Left ventricular dysfunction (n=37)	0
Mitral regurgitation (n=37)	3 (8%)
Pericardial effusion (n=37)	6 (16%)
Normal-sized coronary arteries with irregular borders (n=37)	4 (11%)

IVIG was administered in 29 (76%) cases. Fifty-five percent (21/38) of patients received IVIG within 10 days of illness while 21% received IVIG after the 10th day of illness 13% between 10 and 14 days of illness. The dose of IVIG given was 2g/kg body weight. One patient was given a second dose of IVIG on day 12 of illness due to development of carditis (tachycardia, muffled heart sounds) and with increased size of left and right main coronary artery. At that time, the patient remained irritable and with recurrence of fever. The patient was eventually discharged on the 17th day of illness, already afebrile. The same patient was readmitted for methylprednisolone infusion (30mg/kg body weight) on day 27 of illness due to increased size of the right and left coronary arteries on repeat echocardiogram. The patient was discharged after three days with a noted decrease in the size of the coronary arteries with resolution of the mitral regurgitation and pericardial effusion.

Nine patients (24%) did not receive IVIG for various reasons. One patient went home against advice; four patients already presented in the subacute phase and were started with an anti-platelet dose of Aspirin (3-5mg/kg body weight) instead. The reason why the remaining four patients were not given IVIG was mainly due to financial constraints. One patient developed adverse drug reaction to IVIG presenting as generalized rashes upon initiation of IVIG infusion. Diphenhydramine and Prednisone at 2mg/kg/day (for 3 days) was given and the IVIG infusion was prolonged. The patient was discharged on day 26 of illness. High dose Aspirin (55-100mg/kg body weight) was started in 26 (68%) of the patients during the acute phase of illness and high-dose aspirin was shifted to low-dose aspirin (3.3 to 6.6 mg/kg body weight) after 49-72 hours of being afebrile. One patient did not receive any Aspirin because of underlying G6PD deficiency.

All patients were discharged after treatment. One patient was readmitted for steroid therapy on day 12 of illness but was discharged thereafter. The mean duration of hospital stay was 3.4 ± 2.18 days. A total of 13 (34%) patients were followed-up. Twelve patients or 32% had their follow-up with their private physician and eight of these pay patients had their follow-up details shared by their attending physicians. For the charity patients, five charts were available for review. The mean duration of follow-up is 9.8 ± 10 months. There was no mortality. Out of the six patients with follow-up and with cardiac involvement, 3 patients had normal repeat echocardiogram and the mean duration to normalization of the echocardiography findings was 6 ± 4 months. One patient was endorsed to another attending physician in the province prior to repeat echocardiogram was done. Four patients had still

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normalizing cardiac abnormalities and still maintained on low-dose aspirin. One patient had enlarged coronary arteries after having dengue encephalopathy. For the patients who had normal ESR/CRP and echocardiography on follow-up, the low-dose aspirin was discontinued. Among those with repeat echocardiography, the mean duration to normalization of abnormal echocardiography findings is 5 ± 3.11 months.

A comparison of our cases with and without cardiac involvement is seen in Table 4 and Table 5. Table 4 shows the patient characteristics of patients with and without cardiac involvement. The mean age for the two groups is similar. However, among those who did not develop cardiac involvement, only 53% are male and the difference between the two groups is statistically different on univariate analysis. The mean duration of fever for both groups is also similar.

The percentages of other clinical features in both groups are also similar for both groups. Table 5 shows the laboratory findings of patients with and without cardiac involvement. On univariate analysis, there is a statistically significant difference between the KD patients with and without cardiac involvement in terms of elevated WBC, decreased hematocrit, and thrombocytopenia but no significant difference with regard to decreased hemoglobin elevated ESR and elevated liver enzymes.

Thirty-nine percent (15/38) of the cases had atypical KD. Most of the atypical cases fulfilled only 3 criteria. Four cases fulfilled only 1 criteria but three of these cases showed dilated coronary arteries on echocardiogram. Seven out of the 15 atypical KD cases presented after 10 days of fever. Inflammatory markers (ESR) were all elevated however six patients presented with platelet count less than 500 thousand.

In this study population, no significant association was seen between duration of fever, gender, age, hemoglobin, platelet count, neutrophils and atypical presentation with the development of cardiac abnormalities in the multivariate analysis (Table 6).

Table 4. Patient characteristics, presenting symptoms and signs in patients with and without cardiac involvement.

Patient Characteristics	Cardiac involvement		*p* value
	Present (n = 22)	**Absent (n = 16)**	
Age, years (mean) (range) (n=37)	2.90 ± 2.44 (2 mos– 8 yrs.)	2.38 ± 1.94 (9 mos– 9 yrs.)	0.342
Sex (n=37)			
Male	17 (77%)	8 (53%)	0.017
Female	5 (23%)	7 (43%)	0.198
Clinical Features (n=37)			
Fever, days (mean) (range)	9.4 ± 5.05 (5– 26)	9.3 ± 5.07 (5– 21)	0.146
Rash	13 (59%)	10 (69%)	0.126
Non-exudative conjunctivitis	17 (77%)	11 (69%)	0.295
Cervical lymphadenopathy	19 (41%)	7 (47%)	0. 500
Erythema of lips & oral mucosa	17 (77%)	14 (88%)	0.156
Changes in extremities	15 (68%)	13 (82%)	0.205

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Table 5. Laboratory parameters in patients with and without cardiac involvement.

Laboratory Parameter	Cardiac involvement		*p* value
	Present (n = 22)	**Absent (n = 16)**	
Laboratory Findings			
WBC (n=36)	15.96 ±6.02 (5.55-28.1)	16.28 ±1.42 (8.4– 28.64)	0.006
Neutrophils (n=36)	0.65 ±0.17 (0.25– 0.87)	0.67 ±0.06 (0.4– 0.9)	0.038
Hemoglobin (n=36)	100 ±9.96 (79-125)	107.8 ±10.3 (88– 126)	0.096
Hematocrit (n=36)	0.30±0.02 (0.24– 0.36)	0.323±0.03 (0.27– 0.37)	0.025
Platelet count (n=36)	532 ±214 (177– 1082)	435.4 ±113 (255– 915)	0.032
ESR (n=21)	14 (100%)	6 (100%)	0.242
CRP (n=21)	15 (94%)	4 (80%)	0.334
AST (n=15)	1 (11%)	1 (20%)	0.049
ALT (n=15)	6 (66%)	3 (60%)	0.106
Chest Radiographs			
Abnormal findings (n=5)	2 (67%)	2 (100%)	0.126

Table 6. Predictors of cardiac involvement on multivariate analysis.

Patient Characteristic or Laboratory Parameter	Odds Ratio (95% CI)	*p* value
Fever > 10 days	1.71 (0.359 to 8.145)	0.389
Male sex	2.55 (0.596 to 10.917)	0.182
Age < 1 year old	3.82 (0.397 to 36.833)	0.228
Hemoglobin <10g/dl	1.03 (0.255 to 4.156)	0.626
Platelet count >500,000/mm	1.33 (0.346 to 5.136)	0.470
Neutrophils >75%	1.38 (0.282to 6.704)	0.506
Atypical Kawasaki disease	2.50 (0.599 to 10.440)	0.178

DISCUSSION

Kawasaki disease occurs in children of all races but was reported to be more common in Japan 3. In the Philippines, there are few studies done for KD. The age distribution, male predominance, and characteristic clinical features seen in our patients were similar to other studies reported in Hong Kong[4], Taiwan[5], and Pakistan[3]. Most cases were seen among children below five years old. The disease is rare among the neonates and infants6 though our studies showed the youngest patient being a 2 month-old infant.

Cardiac involvement is the dreaded complication of KD. The incidence of cardiac involvement in KD has been reported at 25%, but a study done in Pakistan reported 41% incidence of abnormality in coronary arteries among their KD cases. In Japan, there is 13.6% cardiac involvement among their KD patients.7 Locally, the reported incidence in the 10-year review of KD patients in Chinese General Hospital was 25%.8 However, one study done in California showed that Filipino KD patients had higher risk of developing coronary artery aneurysm than KD patients of non-Filipino Asian and Non-Asian descent, with reported incidence of 23.8 percent though the reason for the increased severity risk was not elucidated.[9]

Cardiac involvement was seen in 55% of cases in our study, higher than the incidence reported in other studies. This could be possibly due to a high number of delayed diagnosis and/or misdiagnosis (27%) of our patients. The delayed presentation can be due to under-recognition of the disease in evolution among our physicians. Forty-five percent of patients were initially diagnosed with various diseases prior to their admission for KD.

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The pattern of coronary involvement in our study is similar to other published data, with left main coronary, right main coronary and left anterior descending arteries more commonly involved; and the circumflex branch artery as the least commonly involved vessel. Most of our patients had small-sized aneurysms and only one patient had a medium-sized aneurysm.

Although coronary artery involvement is the most common and most life-threatening cardiac complication in KD patients, other cardiac complications include myocarditis, pericarditis, congestive heart failure, pericardial effusion, mitral or aortic insufficiency and arrhythmias.[10] In our patients, 41% had coronary artery dilatation, 11% had normal-sized coronary arteries but with irregular borders, 10% had pericardial effusion and 5% had mitral regurgitation. A total of 19 patients (51%) had coronary artery abnormalities and this figure is higher than any reported studies. The initial cardiac findings of pericardial effusion, irregular borders and mitral regurgitation resolved in the subsequent echocardiogram studies. The self-limited nature of these findings is consistent with other studies.[3] However, for the cardiac findings of coronary artery dilatation, the time it takes for normalization is longer compared to pericardial effusion, mitral insufficiency and irregular borders of coronary arteries. Long-term studies for these patients with coronary artery dilatation are needed to determine the time it takes for resolution of the cardiac involvement.

Thirty-nine percent of our patients presented atypically and seven of these patients presented after 10 days of fever. Experts categorize atypical KD to patients with fever and having 2 of the five criteria and with coronary artery involvement3 but a study in Japan showed that a child with any 3 of the five criteria (with or without coronary artery involvement) is considered to have atypical KD8. Comparing the data with other studies, there is a higher percentage of patients who presented atypically (39%) as compared to the 1999 Philippine study (21%)8, Pakistan (18%)3 and Japan (18.6%)7.

The possible predictive factors for the development of cardiac abnormalities published in other studies (duration of fever, gender, age, hemoglobin, platelet count, neutrophils and atypical presentation) were not found to be significantly associated in this study population. A high index of suspicion among our physicians may be helpful for early detection and management of KD.

LIMITATIONS OF THE STUDY

The limitation of the study includes having a small number of cases. For a period of two years, only 38 cases were gathered. Not all patients had their laboratory results and the timing of the laboratory determination was not uniform. Furthermore, not all patients had their echocardiography done and not all echocardiography was done by the same diagnostic center/echocardiographer. There was also difficulty accessing the medical records of patients especially their outpatient follow-up records, especially those who follow-up with their private physicians, so most of the data on follow-up was lacking.

RECOMMENDATIONS

For future studies, it is recommended that a prospective study is performed to determine risk factors for cardiac involvement in KD patients. All laboratory parameters and baseline echocardiography should be obtained for all patients, preferably reviewed by a single echocardiographer. Furthermore, long-term studies into adulthood should be done to determine the risk of premature coronary artery

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disease among patients who developed KD in childhood.

CONCLUSION

The incidence of cardiac involvement in patients with KD among children admitted is 59% and among those with cardiac involvement, 68% had coronary artery dilatation, higher than in other published studies. The mean age at diagnosis is 2.67 ± 2.26 years and the male to female ratio is 1.9:1. Mean duration of fever at presentation was 9.23 ± 5.17 days There was no mortality and the mean duration of hospital stay was 3.4 ± 2.18 days. IVIG was administered in 29 (76%) of cases. The initial cardiac findings of pericardial effusion, irregular borders and mitral regurgitation resolved in the subsequent echocardiogram studies after IVIG. The mean duration of follow-up is 9.8 ± 10 months. For the remaining patients with residual coronary artery abnormalities on follow-up, the mean duration to normalization of abnormal 2d-echo findings is 5 ± 3.11 months. Male sex, age less than one-year-old, hemoglobin less than 100, platelet count more than 500 thousand, neutrophils more than 75%, and atypical KD were not significantly related to the development of cardiac abnormalities on echocardiogram. A high index of suspicion among our physicians may be helpful for early detection and management of KD.

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