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KAWASAKI DISEASE IN CHILDREN PRESENTED TO MAKASSED GENERAL HOSPITAL: A SEVENTEEN YEAR REVIEW

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ABSTRACT

Background: Kawasaki disease is an acute febrile illness of early childhood, with about 80% of cases occurring between 6 months and 5 years. It is characterized by fever lasting at least five days and a constellation of clinical features that are used as diagnostic criteria. **Objectives:** To describe the epidemiologic, clinical and laboratory characteristics of Kawasaki disease in children presented to Makassed general hospital between 2000 and 2017 and to compare between the 2 types of Kawasaki disease, typical and atypical, aiming to predict factors likely to affect the outcome of the disease in terms of cardiac complications especially coronary artery aneurysm. **Methods:** This is a retrospective population-based descriptive study using hospital discharge records of Kawasaki disease diagnosis of children younger than 18 years of old in Makassed General Hospital between 2000 and 2017. **Results:** Between 2000 and 2017, Ninety Eight (98) patients were diagnosed as having Kawasaki Disease, of which 44% (n=43) fulfilled the complete criteria classified as Typical Kawasaki disease and 56% (n=55) were classified as atypical Kawasaki. 75.5% (n=74) of patients were aged between 1 and 5 years and 70.4% (n=69) were of male gender. 13.3% (n=12) of patients had positive EBV-IgM and 12.2% (n=11) had positive Mycoplasma titer. 5.5% of patients with atypical KD (n=3) and 4.7% of patients with typical Kawasaki (n=2) had dilated coronary artery on echocardiography (p=0.21) and 3.6% of patients (n=2) who had atypical Kawasaki disease, had coronary ectasia on echocardiography. All our patients received IVIG for treatment with 100% response to treatment. And finally the number of patients diagnosed with Kawasaki disease increased from 2 patients in 2000 to 16 cases in 2015, 15 cases in 2016 and 13 cases in 2017 which may attribute to increased awareness for the early diagnosis of the disease. **Conclusion:** Kawasaki Disease has been more frequently diagnosed over years in our institution. It is more prevalent in males than in of females between 1 and 5 years of age. Infants less than one year have few clinical features of the disease thus diagnosed with atypical Kawasaki and are at higher risk of having coronary artery lesions. Moreover, patients with KD may have concomitant infection that does not preclude the diagnosis of Kawasaki disease.

KEYWORDS: Kawasaki Disease, Typical KD, Atypical KD, Coronary artery lesions.

INTRODUCTION

Kawasaki disease (KD) is an acute febrile illness of childhood that is characterized pathologically by vasculitis of medium-sized, extraparenchymal arteries, involving the coronary arteries. It was first described in 1967 by a Japanese pediatrician, Dr Tomisaku Kawasaki, as mucocutaneous lymph node syndrome. It is seen worldwide with the highest incidence occurring ina Asian children.[2] It is the leading cause of acquired heart disease in developed countries, whereas rheumatic heart disease continues to dominate the developing world.[1] The natural history, treatment, and sequelae of untreated KD are now well described. However, the etiology remains obscure, hampering efforts to develop a diagnostic test and targeted treatments.

In addition to fever, KD is characterized by 5 principal clinical criteria: bilateral non-exudative conjunctival injection with limbal sparing; erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; edema and erythema of the hands and feet; rash of various forms (maculopapular, erythema multiforme, or scarlatiniform); and nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm

The diagnosis of KD is based on the presence of characteristic clinical signs. For Typical KD, the diagnostic criteria require the presence of fever for at least 4 days and at least 4 of 5 of the other principal characteristics of the illness. In atypical or incomplete KD, patients have persistent fever but fewer than 4 of the 5 characteristics.

In these patients, laboratory and echocardiographic data can assist in the diagnosis. Incomplete cases are most frequent in infants, who, unfortunately, also have the highest likelihood of development of Coronary Artery Aneurysm. Establishing the diagnosis with prompt institution of treatment is essential to prevent potentially devastating coronary artery disease.

The incidence of KD is greatest in children who live in East Asia or are of Asian ancestry living in other parts of the world. In the United States, the first case series was described by Melish in 1976.[3] Currently, more than 60 countries in Asia, the Middle East, the Americas, Africa, and Europe have reported KD cases.[4] The incidence in underdeveloped countries is largely unknown and ascertainment may be incomplete. Many nations around the world have demonstrated an increase in the number of children diagnosed with KD since the early to mid-2000s.[5,6] In Korea, nationwide surveys of KD have been conducted every 3 years since the 1990s.[7] A questionnaire was sent to all hospitals that had a pediatric residency program. During 2006–2008, the average annual incidence of KD in Korea was 113.1 per 100 000 children younger than 5 years. This is the second highest incidence of KD in the world. KD incidence has also been increasing in Korea since 2000. An epidemiologic study of KD in Taiwan was conducted using the database of the National Health Insurance system, which covers most medical care costs of the Taiwanese population.[8] During 2003–2006, the annual incidence of KD was 69 per 100 000 for children younger than 5 years in Taiwan. This rate was the third highest in the world. A retrospective epidemiologic study of KD was conducted using the National Registry, which included data from all major cardiac referral centers in Thailand.[9] The incidence of KD in 1998–2002 ranged from 2.12 to 3.43 per 100 000 children younger than 5 years. An epidemiologic study was conducted using data from 1 tertiary hospital that provided services to all children in Chandigarh, North India.[10] The incidence of KD was 0.51 per 100 000 children younger than 15 years in 1994. The incidence was calculated for children younger than 15 years because the median age of this study population was older. The incidence of KD showed an increasing trend during 1994–2008.

In Lebanon, a prospective survey of a group of children carriers (or at high risk) of an IHD (n: 156) recorded over a period of six years, between May 1st, 1999, and April 30th, 2005, at the National Register of Pediatric and Congenital Heart Disease, Lebanese Society of Cardiology, conducted by Chehab et al. reported that KD is the second leading cause of IHD among Lebanese children 24.4%, after acute rheumatic fever (35.9%).[11] However, no study was conducted to describe the epidemiologic characteristics of Kawasaki disease (KD) and to estimate national KD incidence rates in Lebanon.

Methods

Study design

This is a retro-prospective population-based descriptive study using hospital discharge records with a KD diagnosis for children younger than 18 years selected from the Makassed General Hospital from 2000 to 2017.

Inclusion/Exclusion criteria

We included in the study patients less than 18 years of age, who had fever for five or more days, and had any four of these five clinical criteria: 1) bilateral conjunctival injection; 2) oral mucosal changes, such as injected pharynx, dry cracked lips, or strawberry tongue; 3) changes of the peripheries, such as hand or foot oedema, erythema, or desquamation 4) rash; or 5) cervical lymphadenopathy greater than 1.5 cm in diameter.

Patients with fever of more than five days with laboratory values suggestive of KD (leucocytosis, elevated ESR or CRP…) and received IVIG were also included.

Patients also were included if aneurysm, dilatation, or ectasia of the coronary arteries were seen at echocardiography, even if the other clinical criteria were not satisfied.

Notified cases were excluded if they were duplicate reports or known errors of reporting (that is, diagnosis outside the study time, incorrect diagnoses, or insufficient information supplied).

METHODOLOGY

After obtaining the approval of the Institutional Board review at Makassed General Hospital (MGH), this study included all children hospitalized at MGH and diagnosed to have Kawasaki disease, typical or atypical, according to standard definition and diagnostic criteria between January 2000 and January 2017.

98 children fulfilling the inclusion criteria were enrolled in the study.

Data was collected by reviewing hospital medical records and identifying all children with an International classification and diseases, tenth revision (ICD-10), billing code consistent with Kawasaki disease.

All included subjects had total confidentiality regarding the information filled in the study.

The Data collected in the study included:
- Demographic data (age, sex, place of living)
- Diagnostic criteria of typical and atypical Kawasaki disease; Patients were diagnosed with typical KD if they had Fever for at least five days and at least 4 of 5 of the other principal characteristics of the illness; that is, 1) bilateral conjunctival injection; 2) oral mucosal changes, such as injected pharynx, dry cracked lips, or strawberry

tongue; 3) changes of the peripheries, such as hand or foot oedema, erythema, or desquamation 4) rash; or 5) cervical lymphadenopathy greater than 1.5 cm in diameter.
-Atypical or incomplete KD was identified in patients who had persistent fever but fewer than 4 of the 5 characteristics.
-Use of laboratory values taken at admission and for progression follow up (CBC with differential and platelets, C-Reactive Protein, Erythrocyte sedimentation Rate, Total serum Protein, Live Function tests,…)
-Type of pathogen isolated from blood, urine or stool culture taken at admission.
-Results of serology taken as part of investigations of prolonged fever.(EBV-IgM, CMV-IgM, Widal, Brucella titres….)
-Whether or not the patient received antibiotics for the treatment of the disease assumed to cause the fever.
-Timing of diagnosing Kawasaki disease and decision to start treatment.
- Type of treatment of Kawasaki disease received (IVIG, Steroids, or infliximab, Aspirin…)
- Response of Kawasaki disease to treatment and time after which fever subsided.
- Results of echocardiography done to screen for coronary artery aneurysm.
- Course of patient's illness in hospital and status on discharge.
- Readmission to hospital with same complaint.

Statistical analysis

The Statistical Package for Social Sciences (SPSS, version 24) program was used for data entry, management, and analyses.

Categorical variables were presented as number and percent, whereas continuous variables were presented as mean and standard deviation. Bivariate analysis was carried out by using the chi square for comparing categorical variables, whereas continuous ones were compared using the Student's t-test. A multivariate analysis were conducted to control for confounding variables.

A P-value of <0.05 will be used to indicate statistical significance.

RESULTS

The total number of the Kawasaki disease (KD) cases collected over the 17 years was 100 of which 2 patients were excluded due to insufficient data. So, 98 patients with the diagnosis of Kawasaki disease were enrolled in our study.

44% (n=43) were classified as Typical KD and 56% (n=55) were classified having the Atypical form of the disease. (Fig; 1).

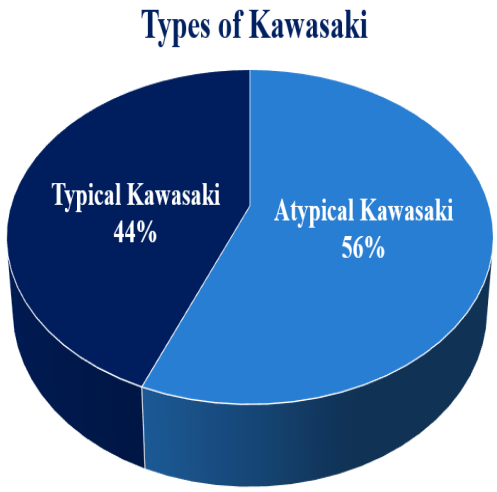

Figure 1: Types of Kawasaki disease.

The majority of cases (75.5%; n=74) were aged between 1 and 5 years, of which 81.8%(n=45) of this age group were diagnosed with Atypical KD and 67.4% (n=29) were diagnosed having typical KD with no statistical significance (P=0.22).

Regarding the gender, KD was more frequent among males {70.4% (n=69)} of which, the majority of cases (76.4%(n=42)) were classified with atypical KD with no statistical significance between the 2 groups (P=0.14).

Table 1: Demographic characteristics.

	Typical KD N=43	**Atypical KD N=55**	**P-Value**
Age <1 year **1-5 years** >5 years	 7(16.3%) **29(67.4%)** 7(16.3%)	 4(7.3%) **45(81.8%)** 6(10.9%)	0.22
Gender Male	 27(62.8%)	 **42(67.4%)**	0.14

Table 2: Clinical characteristics.

	Typical Kawasaki (n=43)	Atypical Kawasaki (n=55)	P-value
Bilateral non-purulent conjunctivitis	33 (76.7%)	29 (52.7%)	0.01
Unilateral cervical L.N	40 (93.0%)	24 (43.6%)	<0.0001
Polymorphous skin rash	38 (88.4%)	17 (30.9%)	<0.0001
Mucous membrane changes	41 (95.3%)	25 (45.5%)	<0.0001
Extremity changes	36 (83.7%)	29 (52.7%)	0.001

Table 2 shows that Mucous membrane changes is the most frequent clinical presentation among the cases of typical KD cases 95.3%(n=41) followed by unilateral cervical lymph node 93%(n=40); however, in the atypical KD cases both the bilateral non-purulent conjunctivitis and extremity changes were the most frequent presentation 52.7%(n=29), showing statistical significance among the 5 variables between the 2 groups.

Concerning the laboratory data, table 3 shows that there was no statistical significance between the typical and the atypical KD groups except for the platelet number where P-value was 0.05.

Table 3: Pathogens associated with KD.

	Typical Kawasaki (n=43)	Atypical Kawasaki (n=55)	P-value
EBV infection	7 (18.4%)	5 (9.6%)	0.23
CMV infection	1 (2.8%)	2 (3.8%)	1.00
Mycoplasma infection	6 (15.8%)	5 (9.6%)	0.52

Table 3 Shows that EBV, CMV and Mycoplasma infections were all found to be associated with our cases of KD with no statistical significance between the two groups.

Regarding the complications of KD upon diagnosis, most of the patients(79.1%) in the typical KD cases and 85.5% of the atypical KD cases had normal echocardiography, followed by Mitral Regurge, more in Typical KD group 9.3%, followed by Dilated coronaries, more in Atypical group (5.5%).

However, Coronary artery Ectasia was only found only in Atypical KD group (3.6%) (Table 4).

Table 4: Imaging results upon diagnosis of KD.

	Typical Kawasaki	Atypical Kawasaki	P-value
Echocardiography			
Normal	34 (79.1%)	47 (85.5%)	
Dilated coronaries	2 (4.7%)	3 (5.5%)	
Coronary Ectasia	0 (0.0%)	2 (3.6%)	0.21
Pericardial effusion	3 (7.0%)	0 (0.0%)	
Mitral regurge	4 (9.3%)	3 (5.5%)	
Ultra-sonography			
Normal	2 (50.0%)	6 (46.2%)	
Hepatomegaly	1 (25.0%)	3 (23.1%)	1.00
Splenomegaly	0 (0.0%)	2 (15.4%)	

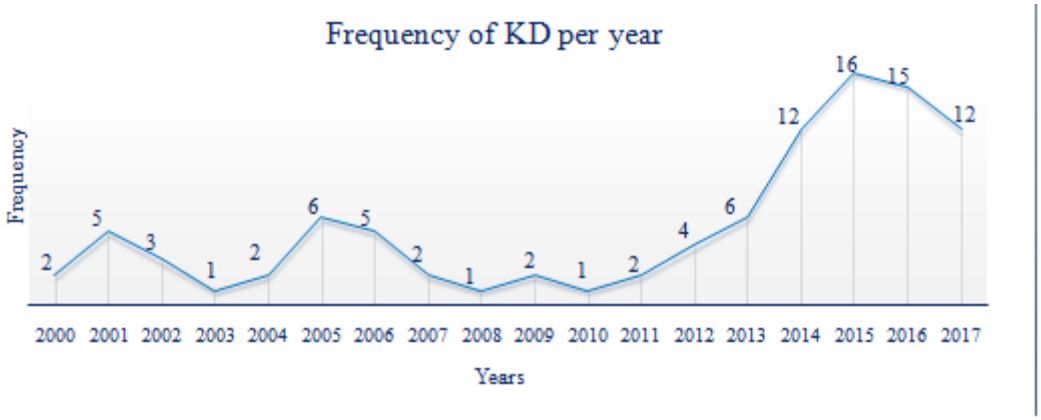

Figure 2: Frequency of KD per year.

Figure 2 Shows the increasing trend in the diagnosis of KD especially over the last 10 years reaching its peak in 2015 where 16 patients were diagnosed in MGH to have KD.

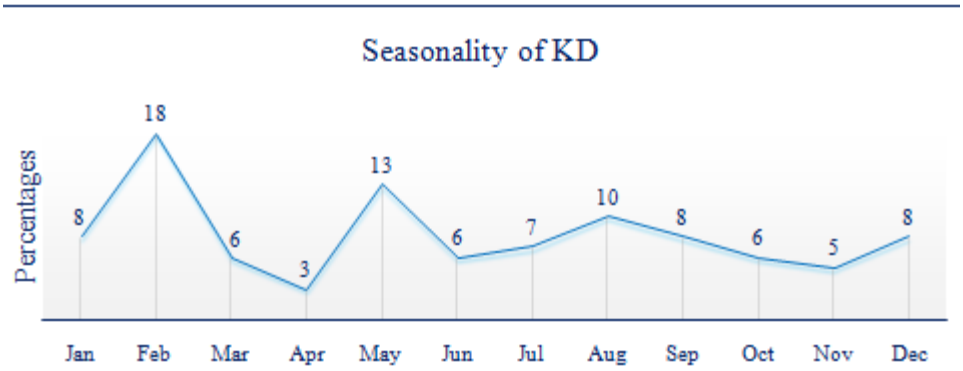

Figure 3: Seasonality of KD.

Figure 3 shows us that KD had 2 peaks, where it was more frequent in winter (during February) & in spring (during May).

DISCUSSION

To the best of our knowledge, this is the first study conducting KD characteristics among Lebanese population. In Lebanon, a prospective survey of a group of children carriers (or at high risk) of an IHD (n: 156) recorded over a period of six years, between May 1st, 1999, and April 30th, 2005, at the National Register of Paediatric and Congenital Heart Disease, Lebanese Society of Cardiology, conducted by Chehab et al. reported that KD is the second leading cause of IHD among Lebanese children 24.4%, after acute rheumatic fever(35.9%).[11] However, no study was conducted to describe the epidemiologic characteristics of Kawasaki disease (KD) and to estimate national KD incidence rates in Lebanon.

Our study population showed that the prevalence of KD is more among the male gender like nearly all epidemiologic studies that show a higher susceptibility to KD in boys (2).

Children between 1 and 5 years of age had the highest frequency among the studied population to have the diagnosis of KD among which the atypical form was more dominant without statistical significance (p=0.22).

Utilizing the Kids Inpatient Database to study trends in KD hospitalizations in 2006, Holman et al reported that more than 75% of all KD-associated hospitalizations in patients <18 yr were recorded in children <5 yr, with a mean age of 3 yr. Children of Asian and Pacific Islander descent had the highest hospitalization rate of 30.3/100,000 children, compared with 17.5/100,000 black, non-Hispanic children, 15.7/100,000 Hispanic children, and 12/100,000 white, non-Hispanic children. The hospitalization rate for KD in 2006 was 20.8/100,000 in children <5 yr of age, which was consistent with the prior 10 yr of hospitalization rates in the United States. In other countries, such as the United Kingdom, Korea, and Japan, the rate of KD seems to be increasing.

In Japan, nationwide surveys have been administered every 2 yr to monitor trends in KD incidence. In 2010, the highest recorded rate thus far of 239.6 per 100,000 children ages 0-4 yr was described, with the highest rate in very young children ages 6-11 months.(2)

Surprisingly, in our study population, the highest incidence of diagnostic criteria among the typical KD

group was mucous membrane changes (95.3%) followed by the unilateral cervical lymphadenopathy (93%) despite the fact the unilateral cervical lymphadenopathy is the least common criterion found in patients with KD (1). However, in the atypical KD group, both bilateral non-purulent conjunctivitis and extremity changes had the highest incidence (52.7%) noting that more than 90% of children with KD develop bilateral non-purulent conjunctivitis.

Both the two groups of KD disease ,the typical and atypical form, meet in the laboratory results; that is, leukocytosis with the mean of 16x10^3 and elevation the inflammatory markers like Erythrocyte sedimentation rate and C-reactive protein, where there was no statistical significance except in the platelet number may be due to the timing of presentation to the hospital and blood withdrawal for testing because it is known that platelet counts are usually elevated by the end of the first week of illness (450,000/x10^3/uL.(x10^9/L) and may evolve into major thrombocytosis, with platelet counts averaging 700,000/x10^3/uL(x10^9) by the third week.

Regarding the pathogens that were found to be associated with our cases of KD, EBV infection was found in 18.4% and Mycoplasma infection was found in 15.8% of the typical form of KD cases which may attribute to a causative relation between these infectious agents and the disease. However, there is no study data in the literature supports this hypothesis.

To date, there is no unique agent has been proven to cause KD. An alternative hypothesis posits that many infectious agents trigger a final common pathway in the genetically susceptible hosts, which is supported by the finding that many patients diagnosed as having KD have documented concomitant infection. The interplay of infection and vascular inflammation has been described in other forms of Vasculitis, such as hepatitis B and polyarteritis nodosa, hepatitis C and cryoglobulinemia, and staphylococcus and Wegner granulomatosis. Accordingly, the hypothesis that infectious agents may trigger the inflammatory cascade in KD has face validity.(1)

In a study from Toronto, more than 30% of children with typical KD had laboratory evidence of at least one infection. Nonetheless, not preclude concomitant infection does not preclude the diagnosis of KD.

While the majority of our patients had normal echocardiography results, the frequency of coronary artery abnormalities was more among cases of Atypical KD where 3 patients vs 2 patients in typical KD group had dilated coronaries, and 2 patents vs. none had coronary artery ectasia and 3 patients vs. 4 had mitral regurge, of note that the 5 patients of the atypical group who had dilated coronaries and coronary artery ectasia were less than one year of age with the youngest patient was 2 months age who presented with a 20 day history of spiking fever and was diagnosed with 3-mm dilated left coronary artery on echocardiography and had a platelet number of more than one million.

This supports what is stated in the American Academy of Pediatrics that infants younger than 6 months are at higher risk for the development of coronary artery lesions, yet often have few clinical features to facilitate the diagnosis. For that reasons, it is recommended that infants younger than 6 months of age who present with fever for at least 7 days of unclear etiology and elevated inflammatory markers have an echocardiogram.

The increasing number of KD cases over the seventeen years in Makassed General Hospital as is shown in figure 2, may be explained by the increased awareness of our physicians for importance of diagnosis and early treatment of KD.

KD in our population study, happened to occur more frequently in February during winter season followed by May in late spring. Seasonal peaks have also occurred in Japan and in the United States, with an increasing incidence in localized areas, suggesting a transmissible vector. In Japan there is a maximum peak in January and a smaller peak in summer. The presence of seasonal variation supports the hypothesis that this disease is caused by an infectious agent. If KD is stimulated by several infectious agents of varying incidence in the peak season, there is the possibility that a number of different peaks are generated per year.[12]

So, the seasonality of the cases may be suggestive of KD epidemic triggered by a single infectious agent.[13]

While there is increased likelihood of KD between parents and children[14] and siblings indicating a genetic cause, our study could not prove this hypothesis since none of or patients had family history of the incidence of the disease.[15]

Our study has some limitations, including the small sample size (n=98) over the seventeen years period and being held in a single referral center. Our study was a also a retrospective cross-sectional study that may have many charting bias. Moreover, the lack of follow-up data of the studied population to evaluate the response of KD to treatment, was of significant limitation, But our study was the first study, to our knowledge, conducting Kawasaki disease in Lebanon over a long period of time.

A further multicenter study with a large population, should be conducted to determine the true prevalence, incident rates and the epidemiologic characteristics of KD among the whole Lebanese population.

CONCLUSION

The present study investigated the epidemiologic, clinical and laboratory characteristics of Kawasaki disease in Lebanese population.

KD incidence is more among males in our study population confirming that male gender is a risk factor for having KD and incidence was also more among children between 1 and 5 years of age simulating Kawasaki disease cases in other parts of the world.

Infants with atypical form of KD are more susceptible to have coronary artery abnormalities, so they need a higher index of suspicion and early echocardiographic imaging is recommended.

Incidence of KD in Lebanon peaks in winter and spring seasons suggesting single infectious trigger.

Concomitant infections like EBV or Mycoplasma do not preclude the diagnosis of KD, so whenever clinical and laboratory data suggest the disease, physician should proceed in the treatment to prevent the fatal cardiac complications of the disease because of the long-term outcomes of KD, the mortality rate with cardiac squeal due to KD is the most important factor in KD management.[16]

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