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Clinical Patterns of Kawasaki Disease and Factors Associated with Echocardiography Abnormalities at Presentation; Libyan Experience

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Abstract:-
Background: Kawasaki disease (KD) is one of the most common vasculitides for children younger than 5 years old. Of unknown etiology that frequently affects small and medium-sized vessels in infants and children. Kawasaki disease is a common cause of acquired heart disease in children. Information on Kawasaki disease and its effects on blood vessels in Libya and other countries are lacking.
Objective: This study aims to describe the demographic, time and clinical aspects of Kawasaki disease (KD) in a Libyan setting. It also examined the associations between the population selected at the initial presentation of acute KD and clinical and abnormal echocardiographic findings.
Methods: This observational, retrospective clinical study was conducted in the Department of Rheumatology and Cardiology, Tripoli, Libya Children's Hospital; From January 2012 to December 2020. Patients with complete and incomplete KD were considered. The diagnostic criteria for KD are based on the recommendations of the European and American Heart Associations.
Results: A total of 71 patients with KD were diagnosed between January 2012 and December 2020, more males (76.1%), aged 1-5 years (67.6%) higher than the younger and older age groups. Most of the problems identified are caused by Tripoli (67.6%) and usually occur for the first time in a public health centre; primary health care, followed by a referral to a tertiary hospital. The time distribution is spread over the seasons; however, the highest rate (40.8%) was reported in spring.
Of the patients exposed to KD, 88.7% met the clinical criteria for full KD. Of the included cases, suspicious heart disease was confirmed in 16.9% by echocardiography, and 8 of 12 patients had vascular changes, 2 patients had dilatation but no aneurysm, and 1 patient had pericardial effusion. All of these were detected at the initial assessment and after 2 weeks of assessment.
The number of abnormalities in 6-month and 1-year control echocardiography decreased to 8 (12.9%) out of 62 and 5 (12.5%) out of 40.
Conclusion: Most patients completed diagnostic criteria to complete KD, and the presence of coronary artery abnormalities is consistent with other international studies. During the follow-up period, all patients were well and fully recovered and there were no deaths.

Keywords:- *Kawasaki Disease, Coronary Artery Abnormalities, Vasculitis In Children, Libya.*

I. INTRODUCTION

Kawasaki disease (KD) is an acute, often self-limiting, mostly necrotizing vasculitis of childhood that usually affects the medium sized arteries particularly the coronaries. [1, 2.] Approximately 15% to 25% of patients have coronary aneurysm or dilatation. Untreated children can develop ischemic heart disease or sudden death. [1,2] Large aneurysms (> 8 mm in diameter) are at risk of rupture, thrombosis and subsequent narrowing of the artery. KD is an important cause of myocardial infarction in children.[4] Other heart diseases may be pericardial effusion; myocarditis and valve insufficiency [4] Therefore, early diagnosis and treatment should be timely and appropriate.

Japanese doctor Tomisaku Kawasaki first described this problem in 1967. Children in Japan are affected more often, the incidence is higher, and appears to increase over time. Children in South Korea and Taiwan are as follows, while the situation in European countries and the United States is less so. In other countries. [1, 2,3]

KD is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, and rash, and cervical lymphadenopathy. Its etiology has not been fully understood for half a century, and it is believed that genetics may still play a role.[3] There are many theories about the pathogenesis of KD, including unknown diseases. These include coronaviruses, parvovirus 19, Staphylococcus aureus, Epstein-Barr virus, chlamydia, and mycobacteria. Staphylococcal and streptococcal superantigens are assumed to be the result of the KD cascade. [1]

KD mostly affects children aged 6 months to 5 years. Seasonal events have been recorded in some countries. Most cases in Japan occurred between January and July. [1] In Chandigarh, the highest incidence occurred between May and October, with the lowest incidence in February. [5.6]

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KD affects boys more than girls, with a difference of 1.36:1 and 1 from male to female 1.62: 1.1.[4]

According to American Heart Association (AHA) guidelines, the optimal treatment is a dose of IVIG (2 g/kg) in combination with acetylsalicylic acid. Despite this initial treatment, most patients do not respond. [7] IVIG unresponsive patients are defined as patients with a fever 36 hours after the end of the IVIG infusion.[7]

KD The most serious complication is CAA's. Factors associated with in CAA's. Some studies included younger age and male gender, treatment duration longer than 10 days, and failure to respond to the first dose of IVIG. Studies reveal also laboratory parameters associated with the development of CAA's such as high level of CRP.[19]

However, there's shortage of clinical information for the Middle Easterner country. Exceptionally small is known approximately KD within the Middle Easterner nations and other Arabic countries. Subsequently, the reason of this study is to identify demographic, time and clinical patterns of Kawasaki illness (KD) and results of KD among Libyan children and to compare our outcomes about with other ethnic populace around the world. To the finest of our information, this was the primary single middle comprehensive think about giving Kawasaki illness information in Tripoli-Libya.

➢ *Objectives*

This study describes the demographic, time and clinical aspects of Kawasaki disease (KD) in the Libyan settings. It also examined the association between the children selected demographic and clinical factors with the presence of abnormal echocardiogram findings at the initial presentation of KD cases.

➢ *Materials and Methods*

This observational, hospital-based retrospective cohort study was conducted at the Department of Rheumatology and Cardiology, Tripoli Children's Hospital, Libya; referrals to private hospitals. The Pediatrics Department has a full cardiology and rheumatology department. All cases were evaluated for heart disease by a cardiologist. From January 2012 to December 2020. Patients with complete and incomplete KD were considered. The diagnostic criteria for KD are based on the recommendations of the European and American Heart Associations. [7,8]

Data analysis was run using the SPSS, version 26. Descriptive statistics was used to present the demographic, time and clinical aspects of KD cases. As all the study variables were categorical, frequency and percentages were used to summarize the data. Several of these variables had missing data, therefore, only their valid percentages were used to present their true pattern (the dominator in the percentage calculation is the total number of valid cases, rather than the total number of cases). To show the annual variation of KD cases over years, a line graph was plotted, and a bar char was used to show the occurrence of cases according to months. The bivariate association between children selected demographic and clinical factors with the echocardiogram findings at initial presentation (abnormal versus normal) were tested using Fisher's exact test and the maximum likelihood ratio chi-square test. Significance level was sat a p value of less than 0.05. Referral to Phi (ϕ) or Cramer's V effect sizes, as appropriate to the size of the corresponding table, was considered for assessing the practical significance of statistically significant findings.

II. RESULTS

➢ *Demographic and time patterns*

A total of 71 cases of KD were diagnosed between January 2012 and December 2020. As seen in Table 1, this disease is more common in males (76.1%)and in the 1-5 age group (67.6%) over young and old age groups. Most of the confirmed cases are from Tripoli (67.6%) and often in one of the public health centers; primary healths care service, then referred to tertiary health care. Regarding the time allocation, the KD case runs the entire season. However, the highest rate (40.8%) was reported in spring. The graph shows the distribution of cases by years. The highest number of CH cases from 2012 to 2020 occurred in 2015 (Figure 1). In these years, April and May have the highest percentage of patients compared to other months (Figure 2).

Table 1: Demographic characteristics of patients and their seasonal distribution (n=71)

Variable	F	(%)
Sex		
1 (Male)	54	(76.1)
2 (Female)	17	(23.9)
Age		
<1year	9	12.7
1-5 years	48	67.6
>5years	14	19.7
Residency place		
Tripoli	48	67.6
Outside Tripoli	23	32.4
Referral place		
Public health care	67	94.4
Private health care	4	5.6
Seasonal pattern		
Winter	18	25.4
Spring	29	40.8
Sumer	11	15.5
Autumn	13	18.3

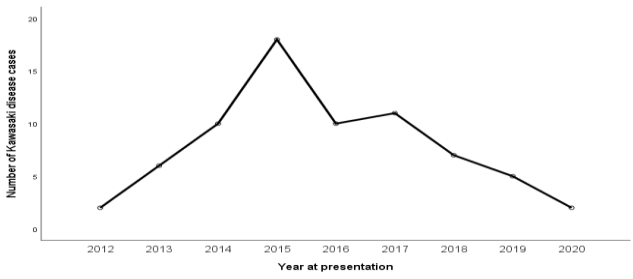

Fig 1: Annual distribution of Kawasaki disease in Libya, 2012-2020

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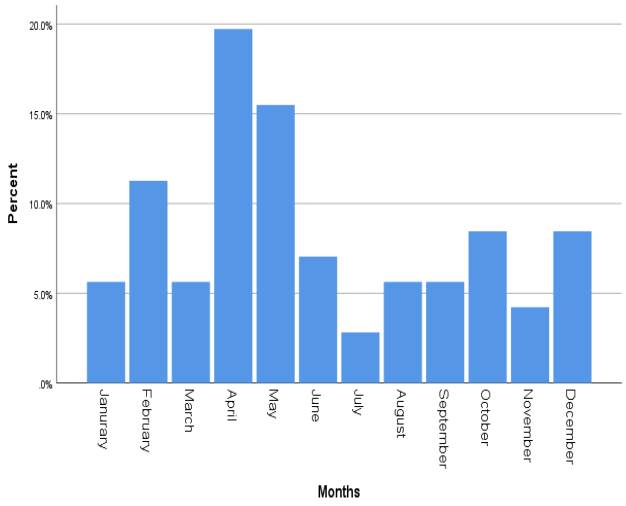

Fig 2: Occurrence of Kawasaki disease cases by months (2012-2020)

➢ *Clinical pattern*

Table 2 shows the clinical pattern of the identified KD cases. While 67.6% of the patients had no provisional diagnosis at presentation, 26.8% were preliminary diagnosed as upper respiratory tract infection. History of antibiotic use was reported in 36 (73.5%) out of 49 cases.

Of all identified cases, 88.7% were typical KD. Fever duration of at least 5 days was reported in 40 (80.0%) out of 50 valid cases. The other three most common clinical features were skin rash in 41 (75.9%) out of 54 cases, skin peeling in 35 (83.3%) out of 42 cases, and non-purulent conjunctivitis in 32 (83.3%) out of 43 cases. Medical records showed cervical lymphadenopathy < 1.5cm in only 22 (64.7%) out of 34 valid cases, oropharyngeal changes in 23 (74.4%) out of 48 cases, and strawberry tongue in 23 (45.1%) out of 51 cases. Other features like oedema of hands and feet were less commonly reported.

Table 2: Clinical profile of patients (n=71)

Variable	F	(%)
Preliminary Diagnosis		
URTI	19	26.8
Acute Gastroenteritis	2	2.8
UTI	1	1.4
Infectious Mononucleosis	1	1.4
Not Yet Diagnosed	48	67.6
Antibiotics use (n=49)		
Used in	36	73.5
Diagnosis		
Typical KD (complete)	63	88.7
Atypical KD (incomplete)	8	11.3
Duration of fever (At presentation) (n=50)		
≥5days	40	80.0
<5days	10	20.0
Skin Rash (n=54)		
Present	41	75.9
Site of rash (n=35)		
All over	30	85.7
Upper Limb	1	2.9
Lower Limb	4	11.4
Skin peeling (n=42)		
Present	35	83.3
Non purulent Conjunctivitis (n=43)		
Present	32	74.4
Changes in oropharynx (n=48)		
Present	23	47.9
Strawberry tongue (n=51)		
Present	23	45.1
Cervical lymphadenopathy > 1.5cm (n=34)		
Present	22	64.7
Oedema of hands and feet (n=46)		
Present	13	28.3
Changes in extremities (n=38)		
Present	1	2.6
Other manifestations (n=49)		
Present	27	55.1

Several clinical variables have missing data (n<71), and the valid frequencies and percentages were reported

Table 3 summarizes the echocardiography findings and some laboratory parameters. At presentation, 12 (16.9%) out of all of the cases had abnormal echocardiography findings. The presence of abnormal findings dropped to 8 (12.9%) out of 62 cases, and to 5 (12.5%) out of 40 cases within the consequence echocardiogram examinations done in 6 months and 1 year, individually.

At presentation, leukocytosis was evident in 32 (57.1%) out of 56 valid cases, with 23 (71.9%) of 32 cases had neutrophilia. Lymphocytosis was found in 9 (28.1%) out of 32 valid cases. Thrombocytosis was reported in 48 (85.7%) out of 56 cases, while anemia was found in only 17 (29.8%) out of 57 cases. Concerning liver function tests, out of 25 valid cases, 4 (16%) had abnormal results.

A few data on urine examination parameters were available in the medical records of the identified KD cases. A total of 12 (80%) out of 15 cases had pus cells, and 9 (81.1%) out of 11 cases had RBCs in urine. Proteinuria was found in only 3 (30%) out of 10 cases.

Table 3: Echocardiography and laboratory patterns (n=71)

Variable	f	(%)
Echo at presentation		
Abnormal	12	16.9
Normal	59	83.1
Echo at 6 months (n=62)		
Abnormal	8	12.9
Normal	54	87.1
Echo at 1 year (n=40)		
Abnormal	5	12.5
Normal	35	87.5
WBC (n=56)		
High	32	57.1

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Normal	24	42.9
Neutrophils (n=32)		
High	23	71.9
Normal	9	28.1
Lymphocytes (n=32)		
High	9	28.1
Normal	23	71.9
Hemoglobin (n=57)		
Low	17	29.8
Normal	40	70.2
Platelets (n=56)		
High	48	85.7
Normal	8	14.3
Liver Function Test (n=25		
High	4	16.0
Normal	21	84.0
Urine-Pus cells (n=15)		
Yes	12	80.0
No	3	20.0

Table 4 summarized the profile of medications used for KD cases. The most commonly used medications were intravenous immunoglobulin, which was used in 68 (98.6%) cases and aspirin in 67 (97.1%) cases, out of 69 cases. Steroids were used only for 22 (34.4%) out of 64 cases, while biotherapy was used only in 1 (1.5%) out of 68 cases.

Table 4: Medications profile (n=71)

Variable	f	(%)
Intravenous Immunoglobulin (n=69)		
Yes	68	98.6
No	1	1.4
Aspirin (n=69)		
Yes	67	97.1
No	2	2.9
Steroids (n=64)		
Yes	22	34.4
No	42	65.6
Biotherapy (n=68)		
Yes	1	1.5
No	67	98.5

Table 5 compares selected demographic and clinical factors between KD cases who had abnormal echocardiographic findings at presentation, and those who had normal echocardiogram. The percentage of cases who had abnormal findings at presentation among patients who live outside Tripoli (30%) was higher than that among those who live in Tripoli (10.4%), and the association between residence place and echocardiographic status at presentation was statistically significant (p=0.047), with an effect size Phi (ϕ) of 0.25, which in turn reflects a moderate practical association (Rea & Paker 1992). However, none of the other factors showed a statistically significant association with the echocardiogram status at presentation. For instance, although the percentage of cases with abnormal findings among cases who had fever for 5 days and longer was higher than that among cases who has shorter duration of fever, fever duration displayed no statistically significant association with the status of echo radiogram at presentation (p=0.557).

Table 5:Comparison of patients who have abnormal and normal echo findings at presentation

Characteristic	Normal echo		Abnormal echo		P value	Effect size (r)
	f	(%)	f	(%)		
Age						
<1yr	7	(77.8)	2	(22.2)	0.485‡	0.133
1—5 yrs	39	(81.3)	9	(18.8)		
>5yrs	13	(92.9)	1	(7.1)		
Sex						
Male	54	(83.3)	9	(16.7)	1.00†	0.011
Female	17	(82.4)	3	(17.6)		
Residency place						
Tripoli	43	(89.6)	5	(10.4)	0.047†*	0.250
Outside Tripoli	16	(69.6)	7	(30.4)		
Antibiotics use (n=49)						
Yes	30	(83.3)	6	(16.7)	0.175	0.224
No	13	(100.0)	0	(0.0)		
Diagnosis						
Typical KD	63	(82.5)	11	(17.5)	1.00†	0.042
Atypical KD	8	(87.5)	1	(12.5)		
Fever (n=49)						
≥5days	34	(85.0)	6	(15.0)	0.557†	0.177
<5days	9	(100)	0	(0.0)		
Skin Rash (n=54)						
Yes	37	(90.2)	4	(9.8)	0.623†	0.077
No	11	(84.6)	2	(15.4)		
Site of rash (n=35)						
All over	27	(90.0)	3	(10.0)	0.646‡	0.162

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Upper Limb	1	(100.0)	0	(0.0)		
Lower Limb	3	(75.0)	1	(25.0)		
Skin peeling (n=42)						
Yes	32	(91.4)	3	(8.6)	0.532†	0.073
No	6	(85.7)	1	(14.3)		
Non purulent Conjunctivitis (n=43)						
Yes	28	(87.5)	4	(12.5)	1.000†	0.046
No	10	(90.9)	1	(9.1)		
Changes of oropharynx (n=48)						
Yes	19	(82.6)	4	(17.4)	0.180†	0.219
No	24	(96.0)	1	(4.0)		
Strawberry tongue (n=51)						
Yes	22	(95.7)	1	(4.3)	0.617†	0.118
No	25	(89.3)	3	(10.7)		
(n=34 Cervical lymphadenopathy > 1.5cm)						
Yes	19	(86.4)	3	(13.6)	0.537†	0.230
No	12	(100.0)	10	(0.0)		
Oedema of hands and feet (n=46)						
Yes	11	(84.6)	2	(15.4)	1†	0.044
No	29	(87.9)	4	(12.1)		
Changes in extremities (n=38)						
Yes	1	(100)	0	(0.0)	1.000†	0.056
No	33	(89.2)	4	(10.8)		
WBC (n=56)						
High	22	(91.7)	2	(8.3)	0.691	0.067
Normal	28	(87.5)	4	(12.5)		
Neutrophils (n=32)						
High	21	(91.3)	2	(8.7)	1.000	0.162
Normal	9	(10.0)	0	(0.0)		
Lymphocytes (n=32)						
High	9	(100.0)	0	(0.0)	1.000†	0.162
Normal	21	(91.3)	2	(8.7)		
Hemoglobin (n=57)						
Low	36	(90.0)	4	(10.0)	0.415†	0.107
Normal	14	(82.4)	3	(17.6)		
Platelets (n=56)						
High	42	(87.5)	6	(12.5)	1.000†	0.000
Normal	7	(87.5)	1	(12.5)		
Liver Function Test (n=25),						
High	20	(95.2)	1	(4.8)	0.300	0.273
Normal	3	(75.0)	1	(25.0)		
Urine-Pus cells (n=15						
Yes	12	(100.0)	0	(0.0)	0.200†	0.535
No	2	(66.7)	1	(33.3)		

P<0.05, † Referring to Fisher's Exact test, ‡ Referring to the maximum likelihood ratio chi-square test

III. DISCUSSION

We conducted the observational, hospital-based retrospective cohort consider of all pediatrics patients with KD (n=71) at Rheumatology and cardiac department in Tripoli children's Hospital in Libya; Tripoli Children Hospital could be a tertiary care hospital. The Department of Pediatrics in this center features a well built up cardiology unit and Rheumatology clinic. All the cases had cardiac assessment by a Pediatric cardiologist. Between January 2012 and 31st December 2020. The American Heart Association guidelines for KD7 were utilized to classify (1) Typical (complete) or atypical (incomplete) [8] and (2) Cardiac abnormalities based on echocardiography performed on all patients by a pediatric cardiologist (see table 1 for cut-offs).

Table 6: Sociodemographic and clinical characteristics of patients with Kawasaki disease (KD) from Libya, Saudi Arabia and Jordan

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Country	Setting N	Time period	Sex ratio	Ethnicity	Typical (complete) KD (N)	Coronary artery involvement (N)
Current study Libya (north Africa)	Single site, University Hospital, Tripoli **(n=71)**	2012-2020	3.2:1	Libyan	63	8
Saudi Arabia (Asia) [16]	Single site, University Hospital, Al Khobar **(n=35)**	1992–2012	1.9:1.0	Saudi (25) Eastern (7) Asian (3)	32	12
Jordan (Asia) [17]	Single site, University Hospital, Amman **(n=34)**	1997–2010	3.9:1.0	Not available	22	20

This study revealed moreover that KD occurred more frequently in male and the male-to-female proportion was 3.2:1 KD occurred mainly in children younger than 5 years and infants, and the normal extent of them was (67.6%)

Male prevalence 3.2:1 is steady with other considers conducted within the Center East region (Saudi Arabia 1.9:1; 4 Jordan 3.9:1; table 5) [4,5]

The onset of KD was more frequent in spring and winter (66%), which is consistent with findings in European reports particular found in Mediterranean area and in neighboring countries[10, 11]. Be that as it may, in reports from Japanese and Korean population in addition to the summer peak, a moment peak was noted during winter.[12, 13] A few East Asian nations, such as China and Taiwan, the most elevated frequency rates were reported amid summer.[14]

Children younger than 5 years old are the foremost frequently affected (81% of cases), comparative to other European nations and countries in West Asia. These findings were distinctive than Japan where the frequency rate was highest among children aged 6–11 months.[12, 14]

The majority of children with KD in our study presented with skin rash (85.7%), which considerably varied in nature. More precisely, maculopapular was the foremost common form, Followed by bilateral bulbar conjunctival injection without exudates (74.4%)which was similar as often as possible seen appearance in a few studies. Whilst bilateral bulbar conjunctival injection without exudates was the first or second most frequently seen appearance in a few studies[10,] in our study it was the fourth most frequent manifestation noted (47%).

Determination of complete and incomplete KD depends on clinical and/or laboratory criteria. The rate for incomplete cases in our study was a low rate, 11.3%, which is reliable with the rate found in a study from Japan where the rate of incomplete disease was only 10%12, but differs from the rate in a study from Spain. Moreover, the percentage of patients with incomplete KD from studies in other Asian nations, such as Shanghai and South Korea, was slightly higher than our findings. In common, the rate of incomplete KD is underestimated and is higher in infants than in older age groups.[10, 15]

The rate of responsiveness to the first dosage of IVIG administered was high (98%), comparable to other studies from East China and Shanghai, Europe, Jordan, the Japanese and the S. Korean population had similar rates of responsiveness.[10, 11,12,13,14,17]

Our findings are also in understanding to results of studies from Japanese population, while in from Korea and Shanghai; the development of CAAs was higher.

The rate of developing CAAs (12.9%) was similar to results from the Japanese populations and other European nations, such as Greece and North Italy, though in Korea and Shanghai, Jordan, the Saudi Arabia (table 6) the development of CAAs was higher. [10,11,12,13,14,16,17]

There were a better number of cases in Saudi Arabia and Jordan of cardiac association being the foremost important feature of KD and CAA developed in ~34% of Saudi. (41%) developed mild or moderate CAA in Jordan (41%). while in our study as it were (11.3%) (Table 6) [16.17]

Risk components for the development of CAAs were assessed in our study and delayed diagnosis; treatment and male gender were recognized as a chance figure. [18]

However, a few other studies have too identified other components as risk components for the development of CAAs, such as gender, postponed treatment, the total duration of fever and blood parameters.[18]

Although our study have a few limitations. The retrospective nature of the study includes children with KD who have been analyzed from 2012 until 2020, which covers over a 9-year period, providing one of the longest Kawasaki datasets described in Libya. Which means it was not possible to collect extra data relevant to Kawasaki disease which a few recorded information may have been missed, such as (ESR, Creative protein liver function test, serum albumin…etc)

IV. CONCLUSION

This retrospective study was the primary report on KD in Libya. Overall our study has comparable characteristics with the previous studies in other nations particularly those sharing the same climatic conditions in European such as Spain and Greece, the Middle East (table 6) and North American nations. Presence of coronary artery abnormalities comprised with other worldwide published studies. All patients successfully completely recovered during follow-

up, and no mortality was documented because majority of cases (98.6%) received IVIG as mainstay treatment.

Recently proposed KD Arab Activity (Kawarabi) should provide future database to assist improve the diagnosis, treatment and outcomes of children with KD over distinctive Arab countries.

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Conflicts of interest: None declared.

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