Diagnosis, Management and Follow Up Of Patients with Kawasaki Disease: A Seven Years Review

Heba Azmi Makki[1*], Amal Shorbasy[2] and Khamis Elessi[3]

[1]Palestinian Board of pediatrics, El-Nasr Pediatric Hospital. Gaza, Palestine

[2]Pharmacist, Master in pharmaceutical science, El-Nasr Pediatric Hospital. Gaza, Palestine

[3]Neurorehab. & Pain Medicine Consultant, Ass't Prof. & head of the evidence based medicine unit in Medical School, IUG

Abstract

Kawasaki disease (KD) is an acute febrile illness in children and is pathologically characterized by systemic vasculitis. It can cause severe coronary artery aneurysms in untreated children. High-dose intravenous immunoglobulin (IVIG), together with aspirin, is clearly effective in resolving inflammation associated with KD and reducing the occurrence of coronary artery lesions (CAL). However, CAL, including transient dilatation, occurs in >10% of patients despite this therapy.

This seven-year case-series review study aimed to shed light on our experience with KD, its clinical presentation; management, outcome and the need for long term follow up of these patients.

There were 14 patients diagnosed as KD during our study period. Seven cases were from Dorra pediatric hospital and 7 cases from El-Nasr pediatric hospital. Males were around 4 times as females with a ratio of 3.7:1 (78.5 % males versus 21.5% females).

Around 50% of cases followed atypical pattern of KD. The vast majority of cases (93%) (13 patients) were below 5 years of age (4 months -5.5 years). Seasonal peak was during winter. Median duration of hospitalization was 7.5 days.

Fever was recorded in all the patients (Mean duration of fever before admission was 10 days), two of cases had fever of unknown origin.

Cardiac involvement was in eight patients of all KD cases. Despite the cardiac complications of these patients, no long term follow up was done for them. So we contacted our patients to come for follow up and ECHO which was normal except for 3 cases showed dilated coronary arteries and announced for another follow up visit after 3 months. All other cases were counseled about their KD condition and the need for long term follow up.

Conclusion: KD is a disease that needs long term follow up for cardiac complications despite normal cardiac examination and ECHO study at presentation and it is not an isolated life event. Diagnosis is mainly clinical and right time diagnosis and management prevents coronary arteries lesions and long term sequelae.

Key words: Kawasaki disease, IVIG, coronary aneurysm, vasculitis, KD shock syndrome, node first KD

Abbreviations

KD: Kawasaki Disease; IVIG: Intravenous Immunoglobulin; CAL: Coronary artery lesions; ECHO: Echocardiography; CAA: Coronary Artery Aneurysm; BSA : Body Surface Area ; CRP : C-reactive protein ; ESR: Erythrocyte Sedimentation Rate ; HDL: High-Density Lipoprotein ; ASA: Acetyl Salicylic Acid; AAP: American academy of pediatrics; AHA: American Heart Association; IVMP: Intravenous Methyl Prednisone ; MI : Myocardial Infarction ; MOH : Ministry Of Health; IUG: Islamic University of Gaza; CBC : Complete blood count ; WBCs : white blood cells; HB : Hemoglobin; US : United state; FU : Follow up;

Introduction

Kawasaki disease (KD), formerly known as mucocutaneous lymph node syndrome and infantile polyarteritis nodosa is an acute febrile illness of childhood. It's the most common cause of acquired heart disease in children in developed countries and 2nd cause in the developing world. The cause of KD remains unknown, but certain epidemiologic and clinical features support an infectious origin. A genetic role in the pathogenesis of KD seems likely (5). KD is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy (4). Diagnosis of KD is by clinical assessment.

KD should be considered in the differential diagnosis of a young child with unexplained fever for at least 5 days and presence of at least four of the five principle features: (a) changes in extremities like erythematic of palms, soles, edema of hands, feet, periungual peeling of fingers, toes. (b) polymorphous exanthema. (c) bilateral non-exudative conjunctival redness. (d) changes in lips and oral cavity like erythema of lips and oral mucosa , lip cracking, strawberry tongue (e) cervical lymphadenopathy (more than 1.5 cm) which is usually unilateral. (4)

Typically, all of the clinical features don't present at a single point in time, and watchful waiting is sometimes necessary before a diagnosis can be made. In these patients, laboratory and echocardiographic data can assist in the diagnosis (5).

For classic KD, the diagnostic criteria require the presence of fever for at least 5 days and at least 4 of 5 of the other principle characteristics of the illness. In atypical or incomplete KD, patients have persistent fever but fewer than 4 of the 5 characteristics. Occasionally, patients with KD may present in cardiogenic shock (KD shock syndrome), with markedly diminished left ventricular function.

KD may presents initially with only fever and lymphadenopathy (node-first KD).(4) In the absence of appropriate therapy, fever persists for a mean of 11 days, but it may continue for 3 to 4 weeks and, rarely, even longer. With appropriate therapy, the fever usually resolves within 2 days (4).

KD can be divided into 3 clinical phases. The acute febrile phase is characterized by fever and the other acute signs of illness and usually lasts 1-2 weeks. The sub acute phase is associated with desquamation, thrombocytosis, and the development of coronary artery aneurysm (CAA), the highest risk of sudden death in patients in whom aneurysms have developed, and generally lasts about 2-3 weeks. The convalescent phase begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically about 6-8 weeks after the onset of illness. (5)

There is no diagnostic test for KD. New diagnostic biomarkers of KD like the 2 urine proteins (meprin a, filamin C) and others still under research (42). Patients usually have characteristic laboratory findings. The leukocyte count is often elevated, with a predominance of neutrophils and immature forms. Normocytic, normochromic anemia is common.

The platelet count is generally normal in the first week of illness and rapidly increases by the second to third week of illness, sometimes exceeding $1,000 \times 10^3/mm^3$. An elevated ESR and/or C-reactive protein value is universally present in the acute phase of illness. The ESR may remain elevated for weeks. (5) Plasma lipids are markedly altered in acute KD, with depressed plasma cholesterol, high-density lipoprotein (HDL), and apolipoprotein A-1. (5)

Concerns have been raised about the possibility of a predisposition of KD to abnormal lipid profile after an acute phase of disease, which can predispose them to premature atherosclerosis later in life (8). A return to normal levels may take years in untreated children, but generally occurs within weeks or months following IVIG therapy. All children with dyslipidemias are classified according to the presence of "high-level" or "moderate-level" risk factors to determine their ultimate treatment.

KD with concomitant aneurysms is one of the high-level risk factor for development of dyslipidemia and KD with regressed coronary aneurysms is one of the Moderate-level risk factor. The (National Cholesterol Education Program (NCEP) recommends an approach toward healthy lifestyle especially in those children at high risk.(24) Whether children who have had KD and normal echocardiography findings throughout their course are at higher risk for the development of atherosclerotic heart disease in adulthood remains unclear. (8).

Echocardiography also may be useful in evaluating children with persistent fever and some features of KD. (4) Cardiovascular manifestations can be prominent in the acute phase of KD and are the leading cause of long-term morbidity and mortality. During this phase, the pericardium, myocardium, endocardium, valves, and coronary arteries all may be involved. (5) Although aneurysms rarely form before tenth day of illness, perivascular brightness, ectasia, and lack of tapering of the coronary arteries in the acute stage of KD may represent coronary arteritis before the formation of aneurysms. Decreased left ventricular (LV) contractility, mild valvular regurgitation (most commonly mitral regurgitation), and pericardial effusion also may be seen in an echocardiogram of a person with acute KD.(4) Coronary artery dimensions, adjusted for body surface area (BSA), may be increased in the 1st 5 weeks after presentation. BSA–adjusted coronary artery dimensions on baseline echocardiography in the 1st 10 days of illness appear to be good predictors of involvement during early follow-up. However, children with non-KD febrile illnesses also have mildly increased z-scores as compared to non-febrile controls, but not to the same degree as patients with KD. Aneurysms have been defined with use of absolute dimensions by the Japanese Ministry of Health and are classified as small (<5 mm internal diameter), medium (5-8 mm internal diameter), or giant (>8 mm internal diameter). A z-score ≥10 is considered giant and hence defines the threshold at which anticoagulation should be initiated.(4,38)

Echocardiography should be performed at diagnosis and again after 2-3 weeks of illness. If the results are normal, a repeat study should be performed 6-8 weeks after onset of illness. If results of either of the initial studies are abnormal or the patient has recurrent fever or symptoms, more frequent echocardiography or other studies may be necessary.

For patients with coronary abnormalities, the type of testing and the frequency of cardiology follow-up visits are according to the patients' coronary status.(5) Risk stratification guidelines are used for Follow up of KD patients.

Risk factors for development of CAA in cases of KD includes being male sex, age less than 6 months, thrombocytopenia on presentation, neutropenia, hyponatremia, hypoalbuminemia, prolonged or recurrent fever and failure to respond to IVIG (6)

Risk Scores can be used for Predicting Aneurysms like HARADA score and others (3) Also, Gunma score , a scoring system to predict intravenous immunoglobulin unresponsiveness in patients with KD includes 2 points each for: aspartate aminotransferase >=100 IU/L, sodium <=133 mmol/L, neutrophil count >=80% of white cells, and days of illness at initial treatment <=4, and 1 point each for: age <=12 months, C-reactive protein >=10 mg/dL, and platelet count <=300,000 /mm³. The range of the risk score is 0–11 points.

Patients with a higher score are at a higher risk of IVIG unresponsiveness and CAL formation.

Once KD is diagnosed, treatment should be started. Delay in therapy can result in serious morbidity and occasional mortality (6). A treatment option includes IVIG as the mainstay therapy with Aspirin. Steroids can also be used in some cases like IVIG resistant

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or non- responding cases. Other treatments like infliximab and etanercept are still controversial.

The mechanism of the beneficial effect of IVIG remains unknown. IVIG appears to have a generalized anti-inflammatory effect with reduction of fever and acute markers of inflammation. (7, 4)

Patients should be treated with IVIG, 2 g/kg in a single infusion (evidence level A), together with aspirin. This therapy should be instituted within the first 10 days of illness and, if possible, within 7 days of illness. (4)

The prevalence of coronary disease, 20-25% in children treated with aspirin alone, is <5% in those treated with IVIG and aspirin within the 1st 10 days of illness(5) The beneficial effects of IVIG are not limited to the prevention of CA aneurysms. Abnormalities in serum lipoprotein profiles may persist for years in untreated patients with KD. IVIG therapy leads to normalization of these abnormalities within months. Similarly, echocardiographic data suggest that another common manifestation of KD, depressed myocardial contractility, may be more rapidly reversed by IVIG. (7) Measles, mumps, and varicella immunizations should be deferred for 11 months after receiving high-dose IVIG. However, children in whom risk of exposure to measles is high may receive vaccination earlier and then be re-immunized at least 11 months after IVIG administration if they have an inadequate serological response.

Acetyl Salicylic Acid (ASA) has been used in treatment of KD for many years. Although ASA has important anti-inflammatory activity (at high doses) and ant platelet activity (at low doses), it does not appear to lower the frequency of development of coronary abnormalities. High-dose aspirin and IVIG appear to possess an additive anti-inflammatory effect. (4, 7) Aspirin is used as recommended by the AHA and AAP, 80 to 100 mg/kg per day and the maximum dose should not exceed 4 gm. per day. Once fever has been absent for 48 hours, patients are generally switched to a low dose of aspirin, 3 to 5 mg/kg per day, for its antiplatelet effect. This low-dose aspirin regimen is continued until laboratory markers of acute inflammation (e.g., platelet count and C-reactive protein) return to normal. Aspirin therapy typically is complete within two months of the onset of disease in children with no CA abnormalities detected by echocardiography. (7)

For children who develop coronary abnormalities, ASA may be continued indefinitely (evidence based level B). (4) Reye syndrome is a risk in children who take salicylates while they are experiencing active infection with varicella or influenza, and has been reported in patients taking high-dose aspirin for a prolonged period after KD. Children who are taking salicylates long-term should receive an annual influenza vaccine. Patients with larger or numerous aneurysms may require the addition of other antiplatelet agents or anticoagulation; such decisions should be made in consultation with a pediatric cardiologist. Acute thrombosis may occasionally occur in an aneurismal or stenotic coronary artery; thrombolytic therapy may be lifesaving in this circumstance.

Corticosteroids have been trialed (using a single pulse dose of intravenous methylprednisolone (30 mg/kg)) as primary therapy with the first dose of IVIG to improve coronary outcomes. Patient's

refractory to initial therapy with IVIG seemed to have a lower risk of developing CA aneurysms if they had received pretreatment with IVMP.

Classification of patients' risk of developing CA aneurysm at presentation with KD (by Gunma score for example) may allow selection of those children who are at high risk of developing CA aneurysm and/or developing recurrent fever after initial therapy. This is the group of children most likely to benefit from adjuvant therapy in addition to routine IVIG. (3,7)

IVIG-resistant KD occurs in approximately 15% of patients and is defined by persistent or recurrent fever 36 hours after completion of the initial IVIG infusion. Typically management in these cases includes another dose of IVIG at 2 g/kg is administered to patients with IVIG resistance. Corticosteroids in varying doses and via different routes have also been used as secondary or "rescue" therapy when fever persists after the first IVIG. Tumor necrosis factor inhibitors, including infliximab and etanercept, have also been given for the treatment of IVIG-resistant disease. To date, there is no evidence of improved coronary outcomes with the use of these medications. .(5)

KD is not an isolated life event and once occurred, patient should be followed up periodically according to cardiac involvement and complications. Long-term follow-up of patients with coronary artery aneurysms should include periodic echocardiography with stress testing and possibly angiography if large aneurysms are present. Overall, 50% of coronary artery aneurysms regress to normal lumen diameter by 1-2 years after the illness, with smaller aneurysms being more likely to regress. All children with a history of KD should be counseled regarding a heart-healthy diet, adequate amounts of exercise, tobacco avoidance, and intermittent lipid monitoring. (5)

Recurrent KD is mostly reported in Japan and the US, occurring in 3-4% and 0.8% of cases, respectively. The risk factors predictive of recurrent KD in a child are: younger age (≤2 years) at the onset, male sex, treatment with IVIG, and longer durations of fever, lower hemoglobin levels [8] and presence of CAA at the first episode. . (31, 35)

Methodology

Our case-series study is a retrospective descriptive review of all pediatric patients diagnosed with KD for the last seven years. Data were collected by reviewing the patients' admission files and outpatient follow up records from El-Nasr and El- Dorra pediatric hospitals from February 2011- up to February 2018, by reviewing the presenting symptoms, fever history, physical examination, inpatient investigations, their treatment and follow up. 14 patients were diagnosed with KD and included in our review.

All the patients who were diagnosed as KD during the study period were taken and their files were reviewed including clinical and laboratory investigations (CBC, ESR, and ECHO).

Our inclusion criteria included children who fulfilled all the criteria of KD and children with atypical presentation of KD. We contacted our patients by telephone. An appointment on 29th March 2018 for follow up visit was given. Clinical assessment was done for

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our patients, blood sampling and laboratory investigations (CBC, ESR, cholesterol and triglycerides) and ECHO follow up also done.

Results

During the last 7 years, a total of 14 patients were diagnosed as having KD. Seven of them were from El-Dorra hospital and 7 cases from El-Nasr hospital. All patients were Caucasians. Males greatly out- numbered females 3.7:1 (78.5 % males and 21.5% females as seen in Figure 1). Around 50% of all cases presented with atypical KD manifestation. The vast majority of cases (93%; 13 patient) were below 5 years of age (4 months -5.5 years), mean age 2 years. Seasonal peak was during winter from October to February. Figure 1
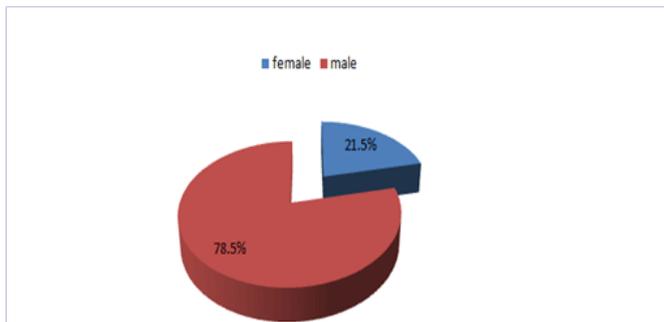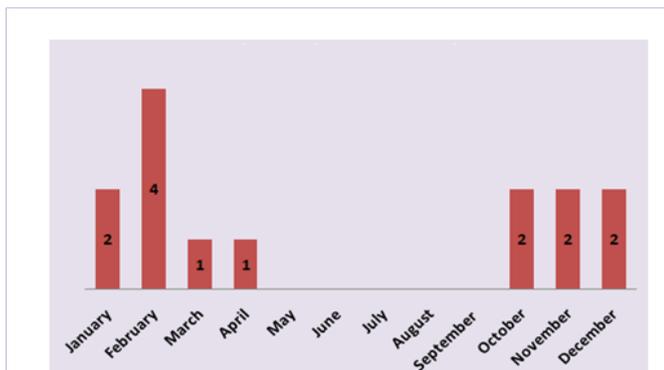

Figure 1: Distribution of KD cases

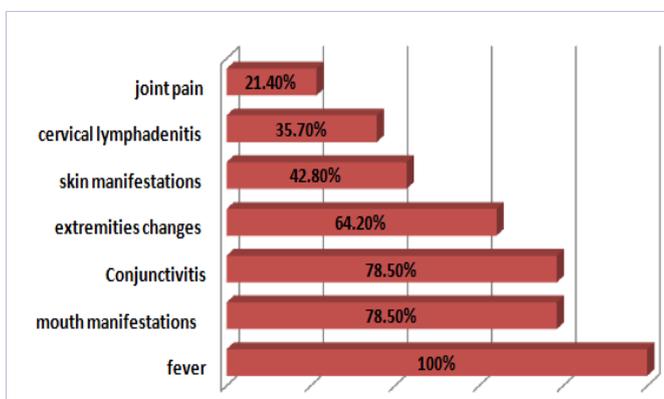**Figure 2:** Distribution of Distribution of cases per month

Figure 3: Frequency of clinical criteria

Median duration of hospitalization 7.5 days .The frequency of clinical criteria for diagnosis of KD: Fever in all the patients with mean duration of 9.7 days with a range of 2 – 25 days, 2 of them had FUO (fever of unknown origin : more than 2 weeks), mouth manifestations 11 cases (78.5%). extremities changes (peeling) in 9 cases (64.2%) and joint pain in 3 cases (21.4%), cervical lymphadenitis 5 cases (35.7%), skin manifestations (rash) 6 cases (42.8%). Conjunctivitis in 11 cases (78.5%). Figure 2, Figure 3.

Other associated symptoms and signs: vomiting 2 cases (14.3%), diarrhea 2 cases (14.3%), joint swelling and arthritis 4 cases (28.6%), hepatomegaly was present in 1 patient (7.1%) only . Diagnosis as KD on presentation was done in 3 cases, while 2 case were diagnosed as meningitis , skin infection in 2 cases and stomatitis in one case, pharyngitis one case, heart failure and pericardial effusion in one case, one case sepsis and 3 cases as pneumonia (two of them with pleural effusion) . Figure 4, Figure 5.
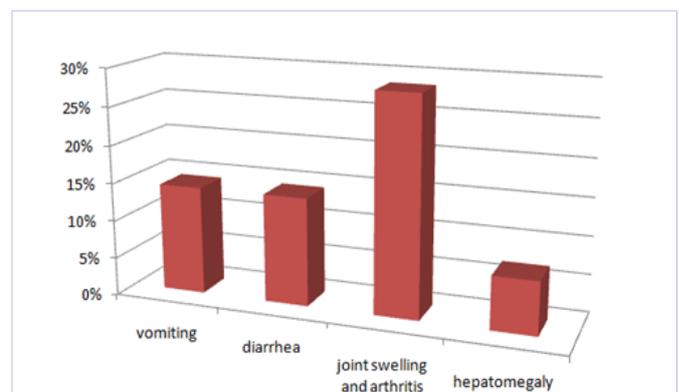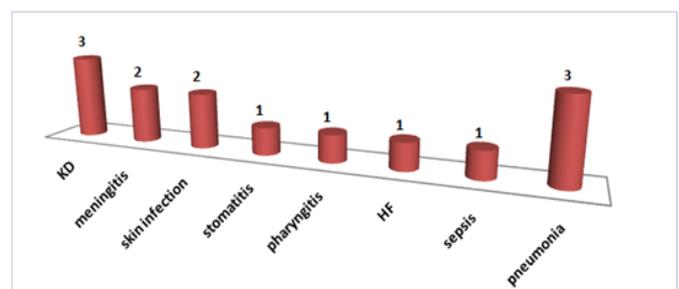

Figure 4: Symptoms and signs

Figure 5: Diagnosis on admission

Regarding laboratory data on presentation: 7 cases had elevated WBC count with mean of $21 \times 10^3 \pm 6$ cell/mm3, anemia in 11 cases (78.6%); (Mean of Hemoglobin was 9 g/dL±1.4). 7 cases had thrombocytosis on presentation (Mean 526×10^3 cell/mm^3) (Range 254-975 cell/mm^3). Regarding inflammatory markers (ESR and CRP), ESR was done on presentation for 12 patients (mean of ESR 85.2 mm/hr ±45.1) with a range of 15-160 mm/hr. and CRP was done for 6 patients all of them were positive. Echocardiogram done in 10 patients on presentation, seven cases (70%) showed normal ECHO findings, 3 cases (30%) had abnormal coronary arteries.

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During hospitalization, there was no change in the WBC count for all KD patients. PLT count was elevated with a mean of 911x 10^3 cell/mm³, ESR follow up during hospitalization was elevated with a mean of 104 mm/hr ± 47 (range 18- 160), Triglyceride level was done for 3 cases with mean 157 mg/dL .

ECHO during hospitalization was done for 7 cases , 2 were normal , 5 cases were abnormal (2 of them was abnormal from presentation and still dilated coronaries, 2 were normal on presentation and became dilated coronaries and one case ECHO done only during hospitalization and showed dilated coronaries. Table 2

Table 1: Investigation results of KD Patients on admission

Investigation	No.of Patients	Normal	Abnormal
WBC	14	7 cases	↑ 7 cases Mean 21 x 10^3 ± 6 cell/mm³
HB	14	3 cases	↓ 11 Cases Mean 9±1.4 (6.2-11.2)g/dl
Platelet	14	7 cases	↑ 7 cases Mean 526 x 10^3 cell/mm³
ESR	12	0	↑ 12 cases Mean 85.2±45.1
CRP	6		6 cases +ve
ECHO	10	7 cases	3 cases

Table 2: Investigation results of KD patients during hospitalization

Investigation	No. of patients	result
Platelet	↑11	Mean= 911 x 10^3 cell/mm³ ± 305
ESR	↑ 9	Mean 104 mm/hr ±47
triglyceride	↑ 3	Mean=157mg/dL
ECHO	7	(2) normal study (5) abnormal

Delay in diagnosis (diagnosis on 10th day or more from occurring of fever) was in 8 cases (57 %). Thirteen patients (92.8%) receive IVIG, dose given 1-2 g/kg (One patient received IVIG three doses and 3 patients received two doses IVIG, nine cases needed only one dose of IVIG(. There were two IVIG-resistant cases. Two cases developed allergic reactions due to rapid infusion of IVIG. One patient receives methylprednisolone due to unavailability of IVIG. Figure 6, Figure 7

High dose Aspirin was received by all the 14 patients during admission with the correct dose. Fever subsided after 1 -10 days from starting KD treatment with a mean of 3.7 days. Shifting from high dose aspirin to low dose aspirin when being afebrile was done for all cases and discharged on the same day of shifting. The dose of Low dose aspirin was correct for 12 cases (3-5 mg /kg once) and incorrect for 2 cases. One patient discharged on Low dose aspirin with clexan and warfarin due to persistent coronary aneurysm. Median duration of continuing Low dose aspirin in patients without cardiac complications was 6 weeks and for patients with cardiac complications was 48 weeks. One case had recurrent KD.

Regarding long term follow up: one case developed recurrent KD at age 4 years, one case developed febrile viral infection and recurrent KD was excluded as criteria wasn't full for diagnosis. One case developed Guillain-Barre syndrome at age 7 years.

The 1st follow up documented visit was after 4-21 days from discharge for 12 cases (85.7%). Data was complete for the patient, including history, physical examination, results of requested laboratory investigations and ECHO was in only 50% of the documented visits. Only one case had periodic follow up visits and 3 other cases were seen one time only after discharge. Counseling about the need for periodic long term follow up for affected children was done for only 2 cases.

Regarding our study visit which included 13 patients. One case was excluded from our study as the family refused to participate in the study visit follow up, children age ranged from 1.5-9 years (mean 4.5 years) . Full history and physical examination were done for them. Cholesterol level ranges from 97-183mg/dL (Mean value 147mg/dL). Triglyceride level ranges from 17-317mg/dL (mean value 86.5mg/dL). Cholesterol and triglycerides are still high for 2 cases from our patients.

ECHO follow up was normal except for 3 cases showed dilated coronary arteries and announced for Follow up visits after 5 months. Other cases without persistent cardiac problems were advised for periodic follow up after range from 1-5 years according to the presence of previous cardiac problems or not.

Discussion

This is the first KD case-series review in the Gaza Strip, which included all the cases diagnosed with KD in the last 7 years (Both the typical types and atypical cases).

As expected, the observed incidence of KD in males is more than in females and most of hospitalized KD cases were under five years of age. In many studies, KD was found to be more common in Winter months (32). On the other hand, KD was found to have seasonal variation in some regions. This may be explained by varying geographic distribution of countries (32). In our study, we found KD seasonal peak in winter season from October to February.

Holman et al reported that more than 75% of all KD-associated hospitalizations in patients <18 year were recorded in children <5 year, with a mean age of 3 years.(5) which is similar to our findings .

Fever, mouth manifestations, conjunctivitis and skin peeling were the most clinical features in many studies (5, 33) and in our study.
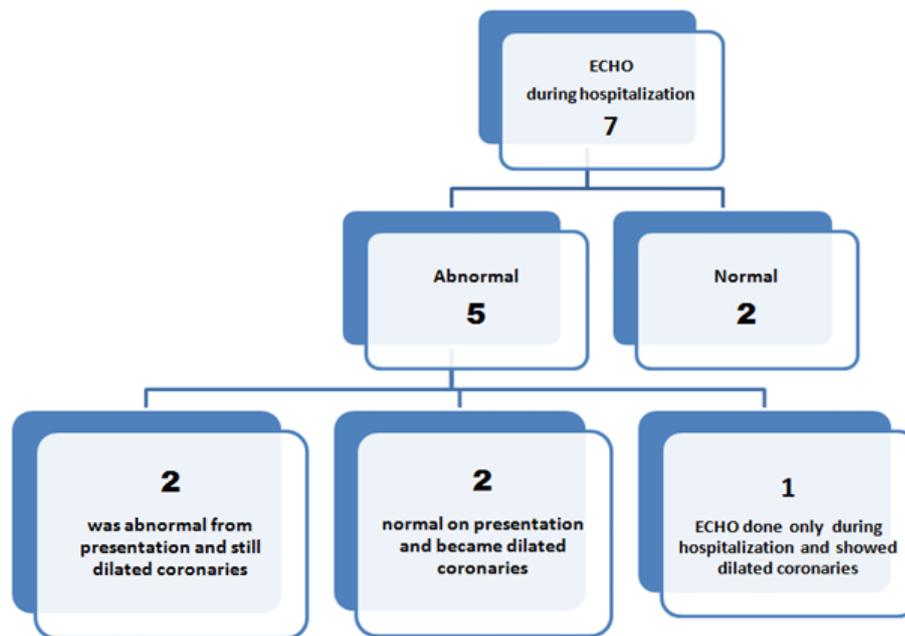
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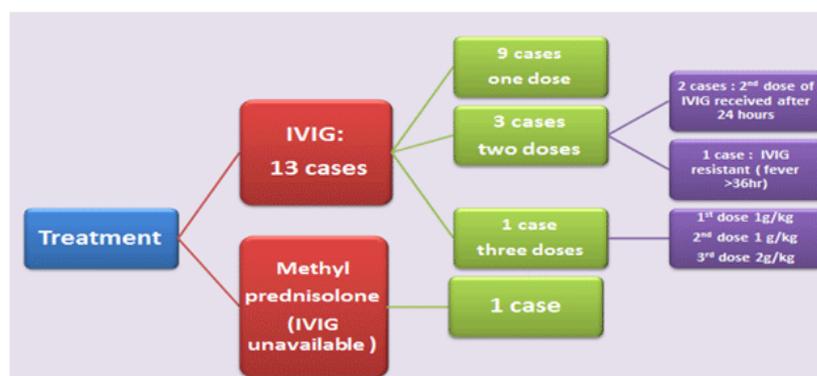**Figure 6:** ECHO follow up during hospitalization

Figure 7: Treatment course during hospitalization

Early diagnosis of KD and early management can prevent development of CAA and cardiac complications later on. Fever is an alarming symptom and should be investigated thoroughly especially if prolonged. In our study, fever mean duration was 9.7 days and this long duration leaded to further search for symptoms and new appearing signs leading to diagnosis of KD. The delay of diagnosis was in eight cases (57%). This delay was because either to delay in seeking medical advice (50%) or delay in diagnosis after hospitalization (50%) that is contributing to increased CAA. Antibiotics were used for 11 patients as 8 patients were not diagnosed as KD early and were managed as infection on presentation. So any patient with fever more than five days should be assessed to exclude KD. The results of our study confirm the need for a high index of suspicion of KD, especially in young infants and patients who present with incomplete KD, in order to identify and treat patients in a timely manner.

The long duration of hospitalization (median 7.5 days) can be explained by the delay in diagnosis in eight cases (after the 10th day of fever) because the features didn't appear concurrently and also because of the long duration of treatment due to IVIG – resistance in one case where the next treatment line is second dose of IVIG or methyl prednisone after 36 hours of the first IVIG infusion. Beside this also IVIG is not always available in Gaza strip and one case was referred to another hospital (Al Najah hospital -West Bank- Palestine) to receive IVIG.

Inflammatory markers elevation is universally present in the acute phase of illness. ESR may remain elevated for weeks. Comparable to other studies (5, 4), inflammatory markers (CRP or ESR or both) also found to be elevated in all the cases.

It's known that in the acute phase of KD there is anemia and leukocytosis. Thrombocytosis start in the acute phase

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but manifest mainly in the sub acute phase (1, 4, 5, 32, 35). Approximately 50 % of patients have WBCs more than 15 x 10^3 cell/mm^3 (4) and this percentage was similar to our findings. Regarding lipid profile Children with KD develop significant disturbance in serum lipid profiles, including elevated triglycerides and low density lipoproteins, and depressed high density lipoproteins. A return to normal levels may take years in untreated children, but generally occurs within weeks or months following IVIG therapy. (4, 7, 8, 12, 13) In our study, lipid profile was taken in only 3 cases during hospitalization as this point may be not taken in consideration during dealing with KD patient. The NCEP recommends an approach toward children healthy lifestyle especially in those children at high risk. Children with history of KD and persistent CAA are categorized as high risk patients and KD with regressed CAA are considered moderate risk. So These children should be kept on healthy lifestyle to keep normal lipid profile in order to decrease the risk of adulthood atherosclerosis and later on angina and MI . ECHO is an important diagnostic tool in evaluating children with KD. It should be done on presentation to rule out CAL because it is noninvasive and has high sensitivity and specificity for the detection of CAL (4). It is better also to do serial ECHO for KD children follow up as CAA not always occur in the acute disease and may develop later in the sub acute or even the convalescent phases.

Treatment with IVIG (2g/kg) within the first 10 days of illness reduces the prevalence of CAA fivefold compared with children not treated with IVIG. Thus, it is desirable to diagnose KD as soon as possible after the criteria are met, in order to initiate treatment and reduce the risk of CAL. (7) IVIG was used in 13 patients , 6 patients (43%) of them received it within the 1st 10 days of illness .

The other 8 cases with delayed diagnosis and delay in initiating treatment (Treatment after the 10th day) had increased incidence in developing CAA (6 of them) (75%). This confirms the association between delayed diagnosis and treatment and CAA.

The cause of not receiving IVIG (methyl prednisone received) in one patient was the unavailability of IVIG. Regarding the number of IVIG doses needed , 9 cases received only one dose, 3 cases received 2 doses. One case received 3 doses (1st and 2nd doses at 1gram/kg and due to no-response , the 3rd dose given 2 g/kg) .IVIG allergic reactions occurred in 2 cases due to rapid infusion. Correct initial infusion rate is 0.5 mg/kg/min and Maximum infusion rate is 4 mg/kg/min. (i. e. 4-6 hours or longer according to the weight of the child) to prevent infusion reactions and complications.

Full dose of IVIG should be given for full therapeutic effect. One case had incorrect infusion prescription of the IVIG (5 g /6h- weight 9kg, correct 18 g slowly over 9 hours).

High dose Aspirin was received by all the 14 patients during admission with the correct dose while the dose of Low dose aspirin was correct for 12 cases (3-5 mg /kg once) and incorrect for 2 cases. One of them prescribed 20 mg /6hrs (weight: 15 kg correct dose 45-75 mg daily) and one prescribed 100 mg once (weight: 6.5 kg correct dose 20-30 mg once daily).

We had one case with recurrent KD. He had all the risk factors for recurrent KD (younger age (9.5 months on presentation) , male sex, treatment with IVIG , longer durations of fever (3 weeks) , lower hemoglobin levels (6.2 g/dL) and presence of CAA at the first episode (had giant aneurysm)).

The ultimate decisions for case management and long term follow up must be made by physicians in light of the particular conditions presented by individual patients. (4)

Frequent follow up visits should be done for patients of KD. An echocardiogram should be obtained early in the acute phase of illness in order to evaluate for coronary artery involvement. Patients also should have repeated clinical evaluations during the first two months following diagnosis of KD to detect arrhythmias, heart failure, valvular insufficiency, or myocarditis.

Table 3 : Risk stratification and the long-term F/U of KD patients

	Risk level	Medical therapy	Follow-up schedule
I	No CA changes at any stage of illness	None after first 6-8 weeks	counseling for cardiology FU at 5- year intervals
II	Transient CA ectasia (resolves within 8 weeks)	None after first 6-8 weeks	counseling for cardiology FU at 3- 5year intervals
III	1 small-medium CA aueurysm in 1 major coronary artery	Low dose aspirin (3-5 mg/kg per day) until regression of aneurysm	cardiology FU yearly
IV	≥ 1 large or giant CA aneurysm, or multiple or complex aneurysms in same CA without obstruction	Long-term aspirin AND warfarin or clexan for those with giant aneurysms	Cardiology FU twice per year
V	CA obstruction	-Long- term low-dose aspirin -warfarin or clexan if giant aneurysm persists	Cardiology FU twice per year

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The relative risk for myocardial infarction (MI) based upon CA abnormalities detected by echocardiogram can be assessed at six to eight weeks. Based upon this risk, guidelines have been developed by the American Heart Association (AHA) and the American Academy of Pediatrics (AAP) for medical therapy, physical activity, and the schedule and content of follow-up visits (Table 3). Children with CA abnormalities generally receive antithrombotic therapy with aspirin, warfarin, or other agents, as well as regular cardiac evaluation.[7,37]

Regarding our study visit which included 13 patients. Full history and physical examination was done for them. Three cases had complains unrelated to their KD and investigated as one case had pharyngitis, one case had staphylococcus skin infection and

one case had leg pain with large irregular café-au-lait spots on Left chest wall and trunk for which fibrous dysplasia was ruled out and pediatric endocrinology was done to rule out McCune-Albright syndrome and recommended follow up periodically.

Cholesterol and triglycerides were found high in 3 cases and counseling was done about keeping healthy lifestyle for those children. Additionally, ECHO follow up was normal except for 3 cases showed dilated coronary arteries and announced for Follow up visits after 5 months. Other cases were advised about the need for periodic follow up after range from 1-5 years according to the presence of previous cardiac problems or not. Patients with regressed CAA were announced for annual follow up and patients without cardiac involvement after 5 years. Figure 8.
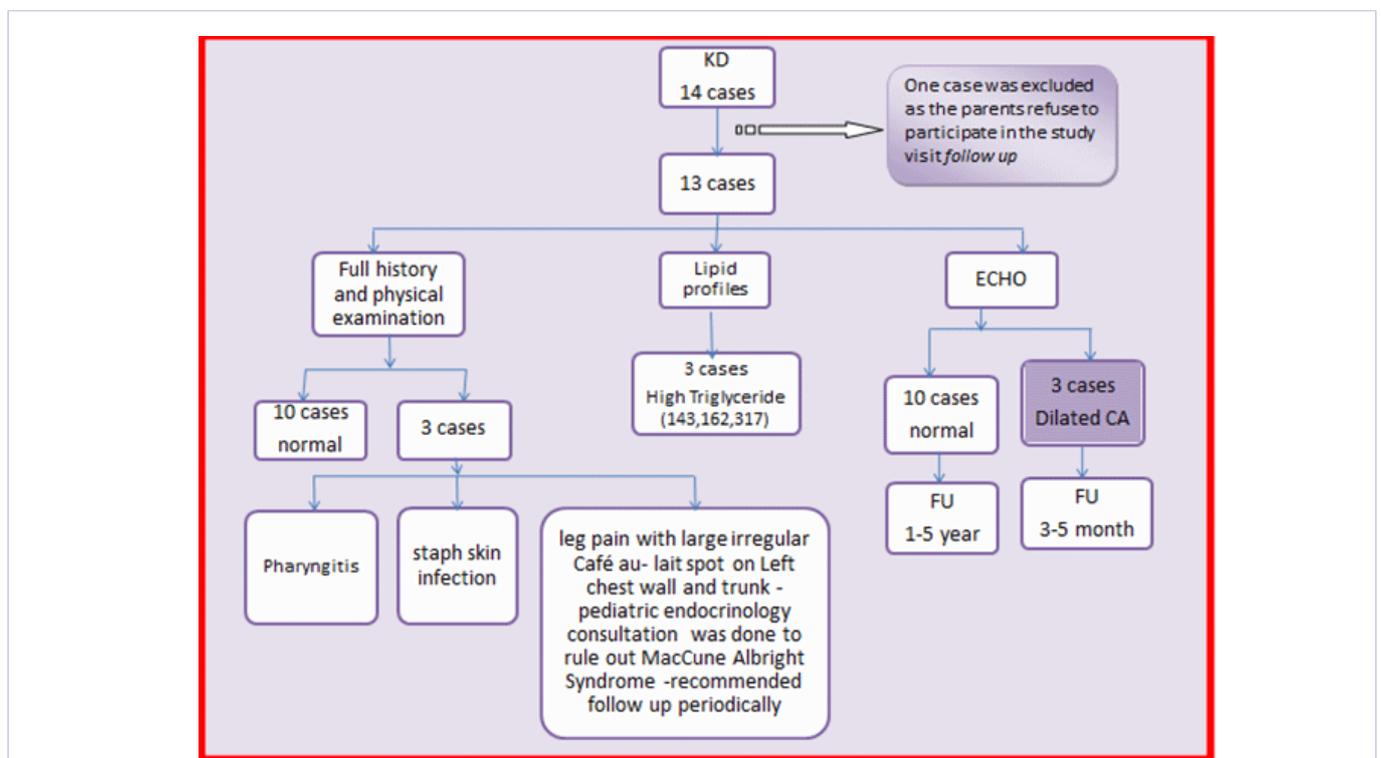

Figure 8: Summarization of our Study follow up visit

Conclusion

KD is a disease that can be intriguing to diagnoses, needs prompt and comprehensive management besides long term follow up to detect any early cardiac complications despite normal cardiac examination and ECHO study at presentation and it is not an isolated life event. Longitudinal follow up should be implemented based on risk stratification and individualized to each patient. Diagnosis is mainly clinical and right time diagnosis and management prevents long term cardiac sequelae.

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