Research Article

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Kawasaki Disease in Children; Clinical Manifestations, Risk Factors and Prognosis, a case Series and Review of the Literature

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ABSTRACT

Background: *Kawasaki disease (KD) is a vasculitis involved small and medium sized arteries and usually is a benign self-limited disease. KD usually presented with fever for 5 days or more with rash, non- exudative conjunctivitis, edema or erythema of hands and feet, unilateral lymphadenopathy or mucosal involvement. If 4 or 5 of the above clinical manifestations are present, the KD is categorized in classic type. Less than 4 above clinical signs categorized as incomplete or non-classic KD.*

Materials &Methods: *In this case study, all of the patients admitted with KD included. In all the patients, data about cases' age, sex, fever duration, hospitalization duration, clinical manifestations associated with Fever, the day of stopping fever following the IVIG treatment, second week's platelet count, the time of the patient's CRP or platelet count became normal, and the result of base line and follow ups echocardiography were gathered.*

Results: *20 cases with KD included in this case study. 75% of the cases were male. The age range of the cases was 13-108 months. The cases mostly presented in winter (11 cases, 55%) or spring (4 cases, 20%). Most of the cases presented as incomplete KD (IKD) (13 cases, 65%). 3 cases have shown abnormal base-line echocardiography at admission day. All the cases with abnormal echo-cardiography presented as diffuse ectasia. No case of aneurysm, thrombosis or occlusion in coronary arteries has detected in the baseline or follow ups echocardiography in the 3 cases or other cases.*

Conclusion: *Although some of our results are like the findings of other studies, designing and performing large multicenter prospective studies is recommended.*

Keywords
Kawasaki disease, Children, Coronary artery lesions, Case study.

Introduction
Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute systemic vasculitis which usually involves small and medium sized arteries; and despite it is usually a self-limited benign disorder, if results in coronary artery disease, it would be devastating. The etiology of the disease is unknown; however, some evidence of a recent infectious disease in history of the patients recommended by some studies [1-3]. Furthermore, it is the most common cause for acquired heart disorder in childhood [4-7]. Generally, it includes 2 types: Classic KD (CKD) is diagnosed in the presence of fever for at least 5 days together with at least 4 of the 5 following clinical criteria:1. Mucosal involvement such as erythema and/or cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa, 2. Bilateral bulbar conjunctival injection without exudates, 3. Rash: includes diffuse polymorphous, maculopapular, or erythroderma in extremities, trunk or perineal rash, 4. Erythema or edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase, 5. Cervical lymphadenopathy with ≥1.5 cm diameter, usually unilateral [6]. Incomplete (non-classic) Kawasaki disease (IKD) occurs when the fever lasting five or more days with two or three

of the above findings. It is noteworthy that all the main clinical manifestations of KD might not present concurrently. Nevertheless, the diagnosis of IKD is challenging and requires a high index of suspicion, because, there is no clear-cut diagnostic criteria which may result in missing on time diagnosis and standard treatment ultimately inducing coronary artery lesions such as dilatation, aneurysms, stenosis, and even occlusion, and is one of the most common acquired heart diseases in young children in developed countries [7-9]. Two-dimensional trans-thoracic echocardiography is the diagnostic imaging modality of choice to screen for coronary arteries involvement.

Materials and Methods

In this retrospective case series all the cases presented with unremitting fever lasting 5 days or more included. Para-clinic tests contained CBC, ESR, CRP, serum Na, K, BUN, Cr, ALT, AST, blood culture, U/A and U/C, ANA, Rheumatoid factor, Double strand DNA (DsDNA), serum C3, C4, CH50, IgG, IgM and IgA, COVID-19, and Influenza A&B PCR have been checked at admission in all the cases. All the cases urgently have undergone a 2 dimensional trans-thoracic echocardiography at admission, 48 hours afterwards and in the next week. The treatment has been ordered after providing IVIG. IVIG as a total dose of 2 gm/kg of the cases body weight, ordered in 10-12 hours duration to each of the cases and all the patients were under supervision with regards to vital signs controlling during the IVIG infusion duration. None of the cases had shown any adverse reactions to the IVIG infusion. Moreover, all the patients have received Aspirin 100 mg/kg of their body weight in four divided doses since admission day which has continued until the fever stopped for 48 hours. Afterwards, the cases have taken Aspirin 2-3 mg/kg of their body weight until the platelet count became normal. For the patients with abnormal echo-cardiography result, an urgent pediatric rheumatology consultation was ordered. CBC, ESR and CRP repeated at the third day of admission and at next week. Follow ups echocardiography has performed again 2 weeks after admission and then every month for 3 months. In cases with normal echocardiography, next echocardiography has performed every 3 months for 1 year. In cases with abnormal previously echocardiography, the interval between next follow ups echocardiography has determined by the pediatric cardiologist and was dependent to the severity of the coronary arteries lesions. Besides, CBC, ESR and CRP have performed every 2 weeks for the cases until their results became normal.

Findings

This case series included 20 patients admitted with five days or more fever and included 15 males (75%) and 5 females (25%). The median age in males was 57 months and in females was 42 months. The youngest patient had 13- month age and the oldest patient was 9- year- old (mean age 54 months). The mean age of cases in CKD was 47 months and in IKD was 62 months. 7 cases (35%) were above 6- year- old and 13 cases (65%) were in 1-6 year- old range. Most of the cases presented with IKD (13 cases, 65%) and the others (7 cases, 35%) admitted with CKD. None of the cases had unilateral cervical lymphadenopathy more than 1.5-centimeter diameter, however, multiple cervical lymphadenopathy less than 1 cm diameter, unilateral or bilateral, in 10 cases, sub-mandibular lymphadenopathy in 3 cases, and/or mesenteric adenophathy in 3 cases, detected which have confirmed with cervical or abdominal ultrasonography. Furthermore, history of upper respiratory infections including coryza, weakness, malaise, lassitude, loss of appetite, nasal obstruction or discharge, dry or productive cough, headache, earache and/or sore-throat in 2-3 weeks before admission were positive in 14 cases, which 10 cases had concurrent lymphadenopathy; 4 cases only had complaints of upper respiratory

Table 1: The cases demographic and clinical criteria.

Patient Number	Age (months)	Sex	Fever (days)	Rash	Ophthalmic involvement	Hand & feet involvement	Mucosal lesions	Subungual peeling	Perineal lesions	Admission month	Kawasaki disease type
1	13	male	7	-	+	-	+	+	+	Dec	classic
2	19	male	14	+	+	-	+	+	-	Dec	classic
3	19	male	7	-	+	+	+	-	-	Dec	non classic
4	20	male	6	-	+	-	+	+	-	Aug	non classic
5	24	female	7	-	+	+	+	-	+	Dec	classic
6	26	female	7	+	-	-	+	+	+	Jul	non classic
7	39	female	7	+	+	-	+	+	+	Apr	classic
8	40	male	10	-	+	+	+	+	-	Feb	non classic
9	48	female	10	+	-	+	+	+	-	Jul	non classic
10	60	male	10	-	-	-	+	+	-	Jun	non classic
11	60	male	7	+	+	+	+	+	-	Dec	classic
12	60	male	7	-	+	+	+	+	+	Jan	non classic
13	60	male	21	+	+	-	+	-	-	May	non classic
14	72	female	14	+	-	-	+	+	-	Jun	non classic
15	74	male	5	-	+	-	+	-	-	Apr	non classic
16	76	male	7	-	+	-	+	+	-	Dec	non classic
17	77	male	20	+	+	-	+	+	-	Mar	classic
18	82	male	14	-	-	+	+	+	-	Dec	non classic
19	96	male	20	+	+	-	+	+	-	Dec	classic
20	108	male	6	+	-	+	+	+	-	Jan	non classic

tract infections. History of recent gastroenteritis was positive in 3 cases which one case had gastroenteritis with submandibular and mesenteric lymphadenopathy. In 3 cases, there was no history of recent upper respiratory tract infection, gastroenteritis or multiple lymphadenophathy. 2 cases just have had bilateral multiple cervical lymphadenopathy. One case complained bilateral sub-mandibular lymphadenopathy. The frequency distribution of the rash, bilateral non-exudative conjunctivitis, mucosal lesions, or hands and feet involvement contained 10 cases (50%), 14 cases (70%), 20 cases (100%) and 8 cases (40%) respectively (Table 1).

Sub-ungual peeling which occurred mostly during subacute phase of disease (during the second to third weeks after fever onset) firstly in the digits and then in the toes happened in 16 patients (80%); despite this clinical manifestation is usually classified within hands and feet involvements, because of its importance in diagnosis, this item was separately considered. Furthermore, perineal changes such as desquamation, peeling, erythema or rash has appeared in 5 cases (20%) usually in subacute phase, and was considered as a separate category, as its presentation is probably confirming the diagnosis especially in the IKD, despite it is usually classified in the polymorphous rash category. 11 cases (55%) admitted in winter and 4 cases (20%) presented in spring. According to the fever duration, just one case had history of 5 days' fever. 13 cases had complaints of unremitting fever between 6-10 days. 3 cases had 2 weeks' fever and 3 patients had a history of more than 19 days' fever (Table 1). In our study, 3 cases had admitted with less than 7 days fever and all of them had IKD criteria. The mean duration of fever in 5- year- old or less cases (13 cases) was 9 days and in cases older than 5 year (7 cases) was 12 days. The mean duration of fever in classic cases was 11.7 days and in non-classic cases was 12.1 days. Moreover, the mean duration of hospitalization in cases with CKD or IKD was 5.7 days or 5.6 days respectively. With regard to para-clinical results, all the patients presented with leukocytosis and polynucleosis. Besides, all the cases at admission had abnormal ESR and CRP (Table 2).

In 5 cases (25%), the platelet count was normal at admission and in the following weeks; however, in 15 cases (75%), the platelet count has risen to abnormal level in the second week after admission (Table 2). The weeks have taken for normalizing the CRP or platelet counts of the cases have been shown in Table 2. In general, the hospitalization duration for the cases was less than 6 days in half of the cases and 6-8 days in the others. Generally, 3 cases (15%) had abnormal echocardiography at admission (two cases with IKD and one case with CKD). All the 3 cases had shown ectasia in coronary arteries. After an urgent rheumatology consultation, methyl prednisolone, 2mg/kg in 3 divided doses has started intravenously, daily for all of these cases, until the rising of the CRP has stopped and then, the patients have taken prednisolone 2 mg/kg in 2 divided doses daily per oral which has continued until CRP became normal. Afterwards, prednisolone has tapered with reducing 5 mg daily each week. Fortunately, none of the three cases had recurrence of the fever, resistance to IVIG or occurrence of any other complications in their coronary arteries. Now, after 18 months of follow-ups, the ectasia has improved in the case number 1 and in the case number 4, and their growth and development were normal. In the third case (case number 13), the

Table 2: The cases laboratory tests results on admission, treatment response, first and follow up echocardiography, second week platelet, normal CRP or platelet time, and hospitalization duration.

Patient Number	ESR	CRP	Fever Stop (Day)	2nd week Platelet	Normal CRP (week)	Normal platelet (week)	First echo	Follow ups echo	Hospitalization (days)
1	58	15	2	650000	2	4	diffuse ectasia	improvement	7
2	69	30	2	636000	4	4	normal	normal	8
3	120	150	2	550000	2	4	normal	normal	7
4	86	127	3	700000	8	6	diffuse ectasia	improvement	8
5	68	75	2	680000	2	6	normal	normal	5
6	109	62	2	510000	4	2	normal	normal	5
7	89	29	4	338000	2	N*	normal	normal	7
8	105	15	2	675000	1	4	normal	normal	6
9	120	53	2	750000	4	8	normal	normal	4
10	62	40	2	520000	4	2	normal	normal	5
11	111	14	2	377000	1	N*	normal	normal	4
12	83	61	2	450000	4	N*	normal	normal	4
13	117	94	2	266000	8	N*	mild ectasia	healed	5
14	60	16	3	369000	1	N*	normal	normal	6
15	85	150	2	480000	8	1	normal	normal	5
16	120	40	2	550000	6	2	normal	normal	6
17	72	130	2	520000	8	1	normal	normal	5
18	36	10	2	650000	1	1	normal	normal	6
19	61	120	3	484000	6	1	normal	normal	4
20	75	130	3	550000	6	1	normal	normal	6

N*: not applicable

ectasia has healed after 2 months of follow-ups and his growth and development was normal.

Discussion

In this case series, 20 cases of KD presented with 5 days or more fever; 7 cases of CKD and 13 cases of IKD. Like other studies, most of the cases were males (75%) [4-6,8-12]. Moreover, 75% (15 cases) of the cases were occurred in the winter or spring similar to other researches [1,2,8]. Despite in the USA, most of the cases happened in under 5- year- old children [4,5], 11 cases (55%) of our patients had more than 5- year- old. Although in some of the new reports, it is estimated that almost 25% of the KD patients would develop coronary artery lesions without treatment [13], 15% of our patients (3 cases), similar to a new report in China [14] had shown primary abnormal echocardiography at admission before starting treatment with IVIG and aspirin. Therefore, it sounds occurrence of coronary artery lesions are not dependent to treatment, at least in our patients. In some of the reports, delay in starting IVIG (more than 10 days after fever onset) has been considered as a risk factor for developing coronary artery lesions in the KD [15-18]. In this study, just one case with 21 days of fever before starting IVIG had shown abnormal primary echocardiography at admission, however, in other cases (8 cases, 40%) with more than 10 days of fever onset before receiving IVIG, base-line and follow ups echocardiography were normal similar to a study in Poland [19]. Two other patients with primary abnormal echocardiography, had 6 or 7 days of fever before starting IVIG, therefore, at least in these 2 patients it seems the delay in prescribing IVIG haven't had effects in appearing coronary arteries lesions, in the contrary the results of some other studies [15-18]. Overall, it sounds the few numbers of our cases in addition to Iranians genetic factors and geographical location of the study might explain these differences. Like a study in Korea [20], in our study, 3 male cases (15%) had abnormal base-line echocardiography in acute phase of their KD which 2 of them had IKD, however, none of them has experienced aneurysm, thrombosis, stenosis or occlusion in the coronary arteries or other cardiac complications in follow ups echocardiography. Furthermore, none of the other cases has developed coronary artery lesions after the acute phase. Despite some of the other reports had mentioned higher incidence rate of coronary artery lesions in IKD than CKD cases [9,15], some of researches have shown no differences in occurrence of coronary artery lesions between two types of KD [23,24] similar to our study results; nevertheless, because of the few numbers of our cases with coronary arteries lesions, this estimate needs to be confirmed in a greater number of cases. It is interesting that our 2 cases (case 1 and case 4) with diffuse ectasia at the admission had high platelet counts at the second week after fever onset; despite the few numbers of the cases with this finding, other reports have also mentioned the relationship between the high platelet counts at sub-acute phase and occurrence of coronary artery lesions [8,11,21,22]. As expected, the platelet count is an acute phase reactant like CRP and increases in inflammatory conditions [25] like KD, however, the casual relationship between the platelet counts and development of coronary arteries lesions should be confirmed in the cellular and molecular level by basic studies. Moreover, like some other studies [1-3], positive history of infections like upper respiratory tract infections, gastroenteritis or lymphadenopathy was positive in 17 cases (85%) in 2-3 weeks before their admission, which is in support of relationship of infection and onset of KD. Unfortunately, our financial resources were limited for performing advanced tests for finding the etiology of the recent infections in the cases. The duration of hospitalization in the cases with CKD or IKD was similar (5.7 days versus 5.6 days); however, the period of hospitalization was longer in cases who started IVIG administration less than 7 days versus 7 days or more, after the fever onset (mean: 6.3 days in 3 cases, versus mean: 5.5 days in 17 cases, respectively), similar to the other report's results [18]. As expected, the mean time from the onset of fever to IVIG infusion was longer in IKD versus CKD cases (11 days versus 7 days respectively), because the diagnosis and treatment of IKD cases usually have been delayed as the result of not complete presentation of major criteria of KD, like some other reports [19]. Moreover, non-concurrent appearance of the 5 main diagnostic criteria usually might miss or delay the on-time diagnosis and treatment of IKD. Fortunately, none of our cases had shown resistance to IVIG or recurrence of fever.

Conclusion

Although most of our results are similar to the result of other studies, some of the findings are contradict the other researches' findings. It sounds that genetic background, geographic location of the study, the type of studies, the sample size and different incidence rate of infectious disease in different populations might explain these differences. Nevertheless, with regard to few numbers of our cases and type of the study, it is recommended multicenter prospective cohort studies are performed in children admitted with KD in order to determine the true incidence of CKD and IKD, their risk factors and development of coronary arteries lesions in them. Furthermore, performing more advanced serologic or PCR tests for recent viral infectious diseases at admission is highly recommended for obtaining possible causal relationship between KD in children and their recent infectious background.

Patient Consent for Publication

Written informed consent for publication of the case series data, without any potential identifying information, was provided by the parents of the patients.

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