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Clinical, Laboratory, and Demographic Profile of Children with Kawasaki Disease Admitted to a Tertiary Referral Hospital in Iran

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ABSTRACT

Background and Objective: One of the leading causes of acquired heart disease in the world today is Kawasaki disease [KD], an acute systemic vasculitis in children. The purpose of this study was to identify the clinical and laboratory manifestations of children with KD admitted to the 17th Shahrivar Educational Hospital in Rasht, Iran.

Methods: We retrospectively studied the cases of 75 children with KD who were admitted to the 17th Shahrivar Educational Hospital in Rasht between 2011 and 2018. The frequency distribution of age, sex, seasonal prevalence, clinical manifestations including fever, skin rash, changes in the lips and oral cavity, conjunctivitis, changes in the extremities, and cervical lymphadenopathy; laboratory findings including platelets and leukocyte count, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]; and response to treatment were studied. The obtained data were analyzed using descriptive statistical methods.

Findings: Out of 75 patients, the most common clinical manifestations were fever [100%], skin rash [78.67%], alterations to the lips and mouth [74.67%], bilateral non-purulent conjunctivitis [64%], changes in the extremities [46.67%], and cervical lymphadenopathy [38.67%], respectively. Among 75 patients, 70 [93.33%] had ESR above 40 mm/h, and 63 patients [84%] had high C-reactive protein [CRP]. Sixty percent of children had incomplete Kawasaki disease. Eight of our patients [10.6%] developed coronary heart disease.

Conclusion: In this study, the most frequent principal clinical manifestations were fever, skin rash, and alterations in the oral cavity and lips. Cervical lymphadenopathy had the lowest prevalence. Increased ESR and CRP were also the most common laboratory findings.

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Introduction

Kawasaki disease (KD) is an acute and febrile vascular inflammation syndrome (acute vasculitis) with the involvement of multiple organs. KD is often limited to childhood, with 80% of patients being less than five years old [1]. Compared to whites and blacks, the East Asian group is more likely to contract the disease. Boys are more susceptible and the male-to-female ratio is 1.5 to 1 [1]. Kawasaki disease occurs in all seasons, but it occurs more frequently in the winter and spring. The etiology of Kawasaki disease is not yet known, but epidemiological and clinical findings strongly suggest the role of an infectious agent. The latest accepted hypothesis suggests that the clinical presentation of the disease occurs following severe stimulation of the immune system by an infectious agent in genetically predisposed individuals [2].

Clinical diagnostic tests are used to make the diagnosis of KD easier when specific mucosal and skin changes occur. In some children, the disease presents with incomplete criteria for the diagnosis of Kawasaki disease. Children under one year of age are more likely to develop this disease, also known as atypical or incomplete Kawasaki disease, which is linked to a higher risk of coronary aneurysm [3].

There is no particular test for Kawasaki disease. Laboratory findings of this disease, although nonspecific, still help diagnose the disease. Normal or increased leukocyte counts are associated with increased neutrophils and immature forms of leukocytes. High erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) with a rise in other acute-phase reactants typically appear during the acute stage of the disease and might last for four to six weeks. Normocytic and normochromic anemia are common. In the first week of illness, platelet levels are often normal and rise quickly in the first two to three weeks of sickness, occasionally exceeding 1,000,000/mm3. Anti-nuclear antibody tests and rheumatoid factor are negative. There may be sterile pyuria, a little increase in hepatic transaminases, and pleocytosis of the cerebrospinal fluid [4, 5].

The most serious complication of Kawasaki disease is cardiovascular disease, which occurs in 25% of untreated children. Today, KD is the most common cause of acquired coronary diseases in developed countries [6]. Cardiac complications include arterial inflammation and coronary artery aneurysm, impaired systolic function, pericarditis and pericardial effusion, cardiac arrhythmia, valvular disease, ischemic heart disease, and peripheral aneurysms in arteries other than the coronary artery [2]. Kawasaki disease responds dramatically to high-dose intravenous immunoglobulin (IVIG) given during the active period of febrile illness. Early administration of this drug can decrease the chance of a coronary aneurysm from 25% to less than 5% [7].

The following shows the necessity of studying the clinical and laboratory characteristics of children with Kawasaki disease: 1- This disease is still the most common cause of acquired coronary heart disease. Also, the prevalence of KD, especially in young children, has increased in recent years [8], which may lead to an increase in the incidence of incomplete KD. 2- Rapid diagnosis of the disease is necessary for timely treatment and prevention of coronary artery complications. 3- Multisystemic Inflammatory Syndrome of Children (MIS-C), which appeared with the spread of COVID-19 in children and adolescents, is sometimes mistaken for Kawasaki disease and has made the diagnosis of the disease more difficult. Therefore, this study was conducted with the aim of investigating the clinical and laboratory findings of children with Kawasaki disease admitted to 17th Shahrivar Hospital during the years 2011 to 2018.

Methods

Study Design and Participant

In this descriptive study, the admission data for KD patients at the 17th Shahrivar Children's Educational Hospital in Rasht, Iran, during the years 2011 to 2018 were reviewed. The 17th Shahrivar Hospital is a level III educational, research, and remedial center for children with 120 active beds.

Sample Size and Sampling

The records of all children who were hospitalized with a final diagnosis of Kawasaki

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disease were reviewed by the researcher in terms of Kawasaki clinical criteria and, if confirmed, were selected for the study. The exclusion criteria were the lack of needed information in the patient's records. In the event of a recurrence of the disease, the patient enters the study only once. The diagnostic criteria for KD in this study were five days of fever or more with four or more of the following five clinical signs:

1) Bilateral non-purulent hyperemia of the eyes, 2) Polymorphous skin rash, especially on the torso, 3) Alterations to the lips and mouth (including dryness and redness of the lips, throat, and strawberry-colored tongue), 4) In later stages, scaling around the nails and erythema of the hands and feet, 5) Submandibular lymphadenopathy (at least 1.5 cm in diameter and usually with erythema), unilateral or bilateral. In addition, no other explanation for these signs and symptoms should be found.

Patients were considered incomplete Kawasaki if they met less than four clinical criteria and had an increase in ESR (≥40 mm/h) and/or CRP (≥3 mg/dL); or had a coronary aneurysm; or had no other differential diagnoses and had at least three following laboratory findings: age-related anemia, thrombocytosis, hypoalbuminemia, elevated alanine transaminase (ALT), leukocytosis above 15,000/mm^3, and more than 10 leukocytes/mm^3 of urine [7].

Data Collection

The necessary information extracted from the patients' records, including sex, age, season, clinical symptoms and signs, laboratory findings, drugs used by patients, and complications of the disease was entered into a questionnaire and reported based on descriptive statistics. The clinical manifestations that were examined in the patient files included the diagnostic indicators (polymorphous rash, changes to the lips and mouth, conjunctivitis, extremity changes, cervical lymphadenopathy), as well as additional findings like restlessness, vomiting, abdominal pain, diarrhea, arthralgia, otitis, and purulent conjunctivitis. White blood cells, neutrophils, hemoglobin, platelets, ESR, CRP, alanine aminotransferase (ALT), leukocyturia, serum albumin, and pleocytosis in cerebrospinal fluid were among the laboratory findings that were looked up in the patients' files. The results of every test were recorded in the patient files and completed in the laboratory of 17th Shahrivar Hospital.

Statistical Analysis

The obtained data were analyzed using descriptive statistical methods, including the calculation of frequency, mean, and standard deviation using SPSS version 16 software.

Results

In the present study, 36 participants were eliminated from the study out of the 111 total because their records lacked certain information. Among the 75 patients studied, 45 were male (60%) and 30 were female (40%), with a male-to-female ratio of 1.5 to 1. With a mean (± SD) of 35 ± 19 months, our KD patients' ages varied from 5 months to 10 years. The age distribution of children is shown in Figure 1. As can be seen in the figure, most of the patients were in the age groups of one year and one to two years old. Total patients over 5 years of age were less than any of the above age groups.

Furthermore, out of 75 patients studied, 17 children contracted KD in spring (22.67%), 20 in summer (26.67%), 17 in autumn (22.67%), and 21 in winter (28 %). Sixty patients lived in urban areas (80%) and 15 patients lived in rural areas (20%). All patients were feverish (100%). However, at the time of admission, several patients had no fever, and the mean temperature of patients at the time of admission to the hospital was 38.04°C with a range of 36.3 to 40.5°C. The mean duration of fever in the patients was 6 days before admission (ranging from two to 14 days, which was 5.8 days in complete Kawasaki cases and 6.1 days in incomplete cases).

Twenty-nine patients had cervical lymphadenopathy (38.67%), of which 24 patients had unilateral lymphadenopathy (32%), and five patients had bilateral lymphadenopathy (6.67%).

Fifty-six cases showed alterations to the lips and mouth (74.67%), of which 20 cases had red lips (26.67%), 16 cases had lip fissures (21.33%), 29

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cases had strawberry tongue (38.67%), and 26 patients had oropharynx erythema (34.67%). Thirty-five patients had changes in the extremities (46.67%), of which 14 patients had erythema of the palms and soles (18.67%), 15 patients' hands and feet had dorsal edema (20%), and 15 patients had extremity scaling (20%).

Fifty-nine patients had skin rashes (78.67%), 57 of which had maculopapular rashes (76%), and two patients had erythroderma (2.67%). Forty-eight patients (64%) also had non-purulent bilateral conjunctivitis (Figure 2). All clinical manifestations are shown in Table 1. The main clinical findings in children with incomplete Kawasaki disease are also shown in Table 2. The patient's laboratory data at the beginning of hospitalization are given in Table 3. One case of positive blood culture (E. coli) was observed. Also, two out of 10 patients with pyuria had positive urinary cultures (one case of E. coli and one case of Klebsiella).

In the echocardiography of these patients, 8 cases of coronary artery ectasia (10.6%), including 5 cases of LCA dilatation, one case of LCA & RCA dilatation, one case of LCA & LAD dilatation, and one case of bilateral ectasia (LCA with a diameter of 3.5 mm, Z-Score: 2.79 and RCA with a diameter of 5.3 mm, Z-Score: 8.28), were observed, and 75% of them had incomplete Kawasaki. Also, 11 valvular disorders were reported: one case of mild mitral valve prolapse (MVP), five cases of mild mitral and tricuspid regurgitation (MR & TR), three cases of TR & pulmonary insufficiency (PI), one case of mild PI, one case of mild MR & TR & PI & MVP. Besides, four cases of pericardial effusion were observed.

Ultrasound of patients showed a case of gallbladder hydrops (1.3%), a case of gallbladder-containing sludge, a case of gallbladder with normal wall thickness and increased luminal diameter, and a case of a slight increase in liver size.

We also reviewed the treatment methods and outcomes of patients with Kawasaki disease. All patients were treated with IVIG at a dose of 2 g/kg and aspirin at an anti-inflammatory dose as soon as they were diagnosed, and only 2 cases of resistance (continued fever more than 48 hours after IVIG injection) were observed, which were completely cured after receiving the second dose of IVIG.

Table 1. Clinical findings of observed KD patients

Clinical findings		N (%)
Findings of diagnostic criteria	Polymorphous rash	59 (78.67)
	Changes in the lips and oral cavity	56 (74.67)
	Conjunctivitis	48 (64)
	Extremity changes	35 (46.67)
	Cervical lymphadenopathy	29 (38.67)
Other findings	Restlessness	33 (44)
	Vomiting	24 (32)
	Abdominal pain	9 (12)
	Diarrhea	7 (9.33)
	Arthralgia	4 (5.33)
	Otitis	4 (5.33)
	Purulent conjunctivitis	2 (2.67)

Table 2. Main clinical findings of patients with incomplete Kawasaki disease

Clinical findings	N (%)
Polymorphous rash	32 (71.11)
Changes in the lips and oral cavity	30 (66.66)
Conjunctivitis	26 (57.77)
Extremity changes	14 (31.11)
Cervical lymphadenopathy	12 (26.66)

Table 3. The patient's laboratory data at the beginning of hospitalization

Laboratory value		N (%)
White Blood Cells*	Normal	46 (61.33)
	Increased	29 (38.67)
Neutrophils*	Normal	28 (37.33)
	Increased	47 (66.66)
Hemoglobin*	Normal	24 (32)
	Decreased	51 (68)
Platelet	Normal	46 (61.33)
	Increased (>450000/mm^3)	29 (38.66)
Erythrocyte Sedimentation Rate (ESR), (mm/h)	<20	2 (2.66)
	20-40	3 (4)
	40-100	47 (62.66)
	>100	23 (30.66)
C Reactive Protein (CRP)	Normal	12 (16)
	Increased (>3mg/dL)	63 (84)
Alanine amino-transferase (ALT)	Normal	46 (61.33)
	Increased (45IU/L)	29 (38.66)
leukocyturia (>10 WBC/hpf)	-	10 (13.33)
Serum Albumin (Checked in 18 patients)	Normal	16 (88.88)**
	Decreased (<3g/dL)	2 (11.11)**
Pleocytosis in cerebrospinal fluid (Checked in 21 patients) (>5WBC/mm^3)	-	7 (33.33)**

*Hemoglobin and blood cell counts are determined by age.
** Frequency percentage was calculated in the number of patients who had albumin checked or undergone lumbar puncture.

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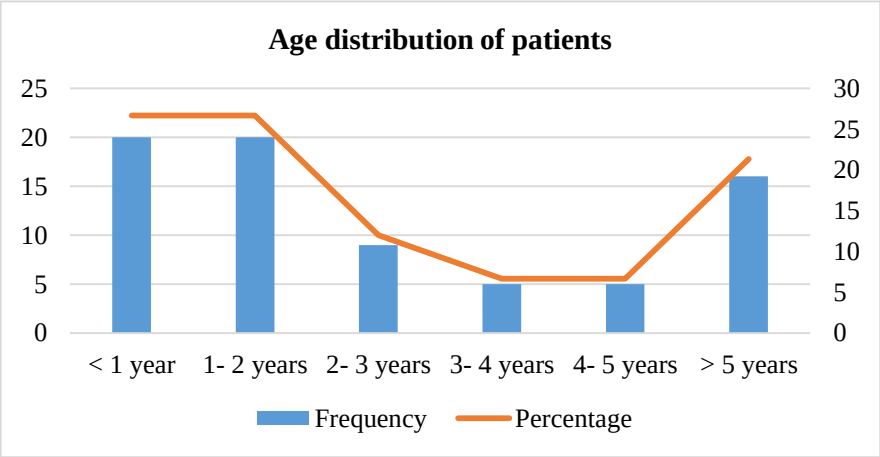

Figure 1. Age distribution of the patients

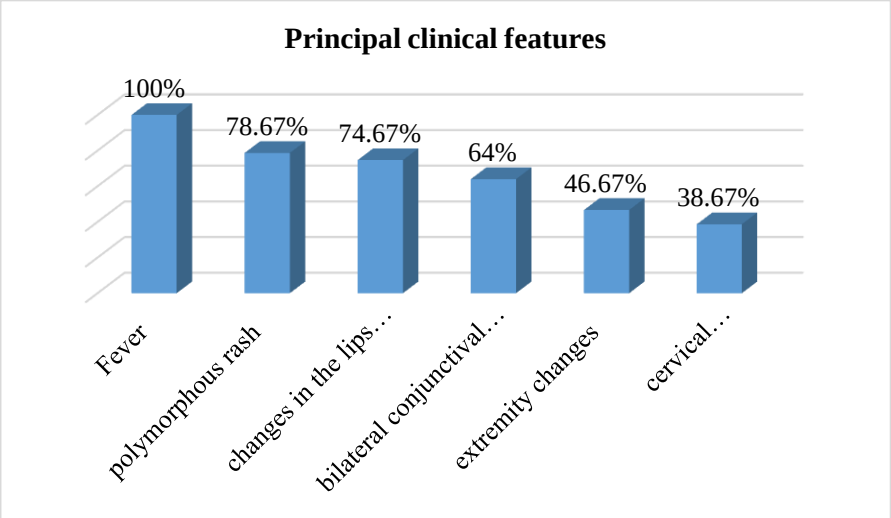

Figure 2. Frequency of patients' principal clinical criteria

Discussion

The objective of our study was to assess the clinical and laboratory findings of children with Kawasaki disease admitted to 17th Shahrivar Hospital during the years 2011 to 2018. Kawasaki illness was discovered in 75 cases, of which 45 were male (60%) and 30 were female (40%), with a male-to-female ratio of 1.5 to 1. The results related to the age distribution of children in the present study are consistent with other studies [8, 9]. In a study on 31,595 Kawasaki patients, Makino et al. showed that the sex ratio (male to female) was 1.34 [8].

The age range of the patients was from 5 months to 10 years old; 78.67% of the patients were less than 5 years old, among which 40 (53%) were under two years old. A recent study by Makino in Japan [8] also showed that the incidence of the disease decreases with age. The mean age of patients in this study was 35 months, which is less than the previous study in this hospital, which was 41.5 months [9], which could indicate the early diagnosis of young children with Kawasaki disease at present or be related to epidemiological changes in influencing factors such as infectious diseases.

Kawasaki disease is seen in all seasons, and so far, no specific seasonal pattern has been shown for this disease, but the disease is more prevalent in Japan and the United States in the spring and winter suggesting the presence of rotavirus in these seasons

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as a possible cause. In China, however, the most vulnerable seasons have been determined to be around the end of spring and the beginning of summer [10]. In the present study, the seasonal distribution of patients was in winter (28%), summer (26.67%), spring (22.67%), and autumn (22.67%), respectively, but no statistically significant difference was present, while in the previous study in this hospital [9], the seasonal prevalence was higher in autumn (37.5%) and then spring (31.5%), respectively. According to this study, most patients lived in urban areas (80%), which is the same as the previous study [9].

In the present study, fever was observed in 100% of cases. The average duration of fever before admission was 6 days (5.8 in complete cases of KD and 6.1 in incomplete cases), which indicates that most patients, even incomplete Kawasaki cases, have been hospitalized at the appropriate time. Skin rash was the second most common clinical finding in our study (78.67%). These findings are consistent with the results of the study by Mahmoudzadeh [11]; but Rahmati [12], Mosayebi [13], and Ayazi [14] reported changes in the mucous membranes of the mouth and lips as the most common clinical manifestations after fever. In addition, some studies in several Asian countries, including China, Mongolia, and Korea, have reported fever and bilateral conjunctivitis as the most common and cervical lymphadenopathy as the most uncommon manifestations of clinical criteria [10, 15, 16]. In the present study, cervical lymphadenopathy (38.67%) had the lowest incidence among the main clinical manifestations. In a previous study at the 17th Shahrivar Hospital in Rasht, Iran, from 1999 to 2007, on children with KD, similar to the results of the present investigation, we demonstrated that skin rashes and alterations in the lips and mouth were the most common clinical manifestations.

In this study, 60% of cases had incomplete Kawasaki disease, which shows a 20.3% increase compared to the previous study in the same center [9]. On the other hand, this finding is consistent with the study of Bressieux-Degueldre and Gündüz [17, 18]. Out of 351 and 39 patients with Kawasaki disease in these two studies, 37.6% and 35.9% were of incomplete type, respectively. This increase may indicate a timely and more accurate diagnosis of incomplete KD cases, especially in young children at present, and on the other hand, it be due to the referral of vague cases of the disease, i.e. patients with incomplete KD, to the 17th Shahrivar referral Hospital in Rasht, Iran. Due to a large number of incomplete KD cases, the classical Kawasaki diagnostic criteria alone are not sufficient to diagnose all cases of the disease, and laboratory tests and echocardiography should be used reasonably; otherwise, they will ignore more than half of Kawasaki patients or delay their diagnosis, which can lead to serious complications. It is also important to note that in developing countries with a high prevalence of infectious diseases such as fever and rash, Kawasaki disease is much more difficult to diagnose.

In our study, elevated ESR and CRP and normocytic normochromic anemia were the most common laboratory findings, respectively, followed by leukocytosis, thrombocytosis, and elevated liver enzymes. In other studies, increases in ESR and CRP were the most common laboratory findings [9, 12, 17]. Therefore, it can be said that the measurement of the above two tests will be very important in the diagnosis of Kawasaki disease and the negation of both of them will be a disadvantage for the Kawasaki disease diagnosis. Positive blood or urine cultures may have a role in the development of KD or may be nosocomial infections.

Abnormal echocardiographic findings were observed in 30.67% of our patients. Eight patients (10.6%) had coronary artery ectasia. Although the prevalence of coronary ectasia has increased compared to our previous study in this hospital, which was 1.6% [9], it was less common than the studies in China, the Netherlands, and Ankara [10, 19, 20]. Six of the eight patients with coronary artery ectasia in this study had incomplete Kawasaki disease, which indicates more attention and a more accurate diagnosis of incomplete Kawasaki disease and its complications by physicians at present.

Only two cases of IVIG resistance (fever that persisted for 48 hours after IVIG injection) were found, and both of those cases were fully healed after receiving the second dosage of IVIG. Evidence with a moderate degree of certainty indicates that

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the use of corticosteroids during the acute phase of KD may be linked to a decrease in coronary artery abnormalities, a shorter hospital stay, and a decrease in inflammatory markers when compared to the use of no corticosteroids, with no serious adverse events or mortality [21].

Limitations of the study

One of the limitations of our study was the lack of long-term follow-up of patients and the lack of evaluation of long-term complications of patients. The retrospective nature of the study and the accuracy of recorded data may also be limitations of the study.

Conclusion

We found a decrease in the mean age of patients with KD and an increase in coronary aneurysms compared to our previous study. Considering the increasing trend of Kawasaki disease incidence in recent years, it is very important to pay attention to the clinical manifestations of the disease and make judicious use of laboratory data, especially in incomplete cases for early diagnosis, timely treatment, and prevention of complications. Therefore, the findings of this study can be helpful. In addition, KD should be considered in children hospitalized with fevers for unknown reasons that do not improve despite appropriate treatment.

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Ethical approval

This research plan was approved by the Vice Chancellor for Research and Technology of the Guilan University of Medical Sciences under No. 94020709 and was approved by the Ethics Committee of Guilan University of Medical Sciences (Approval Code: IR.GUMS.REC.1394.8).

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Conflict of interest

The authors declare that there is no conflict of interest.

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