Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:57-65
DOI: 10.4274/BMJ.galenos.2023.2023.1-5

Research

Kawasaki Disease: 10-year Single-center Experience: Analysis of Clinical and Laboratory Findings with Treatment Approaches

Kawasaki Hastalığı: Tek Merkezde 10 Yıllık Deneyim: Klinik ve Laboratuvar Bulgularının Tedavi Yaklaşımları ile Birlikte Analiz Edilmesi

Ajda Mutlu Mıhçıoğlu, Mehmet Bedir Akyol

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Cardiology, İstanbul, Türkiye

ABSTRACT

Objective: Kawasaki disease (KD) is an acute febrile multisystem disease affecting children between 6 months and 5 years. Coronary artery involvement (CAI) is the most threatened complication of this disease. Therefore, suspicion and early diagnose of the disease is critical. Principal and additional findings are used for diagnosis accompanied by laboratory findings. We evaluated the patients who had the diagnosis and treated for KD at our center.

Methods: Forty-five patients who were evaluated between 2012-2022 with the diagnosis of KD were evaluated retrospectively in our study. Intravenous immunoglobulin (IVIG) administration time, and presence of principal, and additional findings were recorded. Echocardiographic and laboratory findings were also recorded for the study.

Results: Male patients were in predominace, average age was 2 years. Coronary artey involvement was present in 20% and IVIG resistance in 17.8% of the patients. Changes in the oral mucosa and lips were less frequent in the patients with CAI (+), and perineal desquamation was more frequent with IVIG resistance (p=0.039, p=0,033, respectively). All the patients were treated before 10 days (p>0.05) and a second dose of IVIG was administered to 2 patients on the 12th day.

Conclusion: KD should be considered for the patients with longlasting fever, which cannot be explained with other reasons in children under 5 years of age. The relationship between the principal and additional findings with the presence of CAI and IVIG resistance were not mentioned in the literature previously. The similarity of laboratory findings in the groups suggests that laboratory findings may not always guide us about the course of the disease. Although KD may have severe complications, with timely and accurate diagnosis and treatment, the prognosis is good in general.

Keywords: Kawasaki disease, children, coronary artery, intravenous immunoglobulin

ÖZ

Amaç: Kawasaki hastalığı (KH), 6 ay ile 5 yaş arasındaki çocukları etkileyen akut seyirli, ateşli multisistem bir hastalıktır. Koroner arter tutulumu (KAT) bu hastalığın en tehdit edici komplikasyonudur. Bu nedenle hastalıkta şüphe ve erken teşhis çok önemlidir. Temel ve ilave bulgular, laboratuvar bulguları ile birlikte tanı için kullanılır. Merkezimizde KH tanısı alan ve tedavi edilen hastaları değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamızda 2012-2022 yılları arasında KH tanısı ile değerlendirilen 45 hasta retrospektif olarak değerlendirildi. İntravenöz immünoglobulin (İVİG) uygulama zamanı, tanısal ve ek bulguların varlığı kaydedildi. Çalışma için ekokardiyografik bulgular ve laboratuvar bulgular da kaydedildi.

Bulgular: Erkek hastalar çoğunlukta idi, yaş ortalaması 2 idi. Hastaların %20'sinde koroner arter tutulumu, %17,8'inde İVİG direnci mevcuttu. KAT (+) olan hastalarda oral mukoza ve dudak değişiklikleri daha az, İVİG direnci olan hastalarda perineal deskuamasyon daha sıktı (sırasıyla p=0,039, p=0,033). Hastaların tamamı 10. günden önce tedavi gördü (p>0,05) ve 2 hastaya 12. günde 2. doz İVİG uygulandı.

Address for Correspondence: Ajda Mutlu Mıhçıoğlu, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Cardiology, İstanbul, Türkiye
Phone: +90 505 648 64 68 E-mail: ajdamutlu@yahoo.com ORCID ID: orcid.org/0000-0003-0143-4188

Cite as: : Mutlu Mıhçıoğlu A, Akyol MB. Kawasaki Disease: 10-year Single-center Experience: Analysis of Clinical and Laboratory Findings with Treatment Approaches. Med J Bakirkoy 2023;19:57-65

Received: 08.01.2023
Accepted: 17.02.2023

ÖZ

Sonuç: Beş yaş altındaki çocuklarda başka nedenlerle açıklanamayan uzun süreli ateş varlığında ayırıcı tanıda KH düşünülmelidir. KAT ve İVİG direncinin varlığı ile temel ve ek bulgular arasındaki ilişki literatürde daha önce belirtilmemiştir. Laboratuvar bulgularının gruplarda benzer olması, laboratuvar bulgularının hastalığın seyri hakkında bize her zaman yol göstermeyebileceğini belirtmektedir. KH ciddi komplikasyonlarla sonuçlanabilse de zamanında ve doğru tanı ve tedavi ile genellikle prognozu iyidir.

Anahtar Kelimeler: Kawasaki hastalığı, çocuklar, coroner arter, intravenöz immünoglobulin

INTRODUCTION

Kawasaki disease (KD) is an acute febrile multisystem disease of affecting children between 6 months and 5 years (1). It is characterized by a vasculitis effecting medium sized muscular arteries. The disease first was reported in 1967 by a Japanese pediatrician Tomisaku Kawasaki (2). Since then, it has been recognized in many countries all around the world and nowadays it is the leading cause of acquired heart disease in children who are living in developed countries (1,3). The incidence of KD is approximately 330.2/100,000 in Japan and 19.7/100,000 in the USA (2). From Turkey, there has been limited published data therefore we only have the knowledge that it constitutes 9% of the childhood vasculitis and it is the second most prevalent vasculitis in Turkey (4).

The ethiopatogenesis of the illness is still unknown. Infectious agents and immunological abnormalities are blamed (1). Twins have an increased risk of KD; therefore, genetic tendency is thought to play an important role in the ethiopatogenesis (5).

Coronary artery involvement is the most threatened complication of this disease (6). Therefore, suspicion and early diagnose of the disease are critical. There is not a specific diagnostic test to determine the diagnosis of KD (6). The diagnosis of KD is made by using clinical criteria and excluding the other clinical diseases such as viral, bacterial infections, toxin-mediated and hypersensitivity reactions, and rheumatic disease (2,7). Longlasting fever, which is resistant to antipyretic drugs, is the main complaint of this illness. There are 5 principal findings for the diagnosis of KD. These findings are (1,2,5);

a) Bilateral non exudative conjoctival hyperemia,

b) Mucosal changes in the lips and oropharynx, including hyperemia of the oral mucosa with red and dry lips accompanied with fissuring and redness of the tongue like strawberry,

c) Polymorphic rash-like maculopapular diffuse erythema, urticarial exanthema, and erythema multiforme-like lesions without vesicle or bullae formation except bacillus Calmette-Guérin (BCG) inoculation site,

d) Changes in the peripheral extremities: Erythema and edema of the hands and feet,

e) Cervical lymphadenopathy, which is unilateral, firm, non-fluctuant, and painful with a size bigger than 1.5 cm.

There are two types of KD diagnosis: complete and incomplete forms. The complete form consists of fever longer than 5 days and the presence of at least 4 of the 5 principal findings. The incomplete form consists of fever duration shorter than 5 days accompanied with 2 or 3 of the principal findings, supported by laboratory or echocardiographic findings (8,9).

Laboratory findings are; leukocytosis with a shift to left, elevation of erythrocyte sedimentation rate, and C-reactive protein (CRP). The elevation of platelets (PLT) (nearly 700,000 up to 1,000,000/mm^3), decrease in hemoglobin (Hgb) levels, proteinuria, steril pyuria, elevation in transaminase levels, and elevation of biluribin levels (9-11).

Additional findings can be classified as: urethritis, hydrocele, phimosis, abdominal pain, vomiting, diarrhea, hydrops of gallbladder, paralytic ileus, pancreatitis, hepatitis, irritability, facial palsy, limb paralysis, febrile convulsion, encephalitis, and encephalopathy, behavioral changes, aseptic meningitis, sensorineural hearing loss, arthritis, arthralgia, sneezing, cough, pleural effusion, empyema, peri bronchial interstitial infiltrates, small pustules on the knees, elbows and buttocks (1,2,12).

KD has three phases. The findings and laboratory parameters differ between these three phases. The acute phase is the first two weeks of the illness when the patients have high fever accompanied with the other principal findings (2). The subacute phase begins after the fever resolves, and it prolongs for 4 weeks. During this phase, patients have desquamation of tips, arthralgia, and abnormal laboratory findings. The highest risk for coronary artery aneurysms (CAAs) is present in this phase. The convalescent phase is the second month of the illness. The risk of coronary artery involvement is lower during this period (2). The clinical symptoms are absent during this period. Patients are usually referred to hospital through the acute and subacute phases when it is the most risky period for coronary artery involvement (2).

Treatment consists of intravenous immunoglobulin (IVIG) with a dose of 2 gr/kg/day in one infusion of 10-12 hours and aspirin treatment at anti-inflammatory dosage (1,2,10,13). 10-15% of the KD children have recurrent or persistent fever at least 36 after the first dose of IVIG, which is defined as IVIG resistant (1,10,11,13). A second dose of IVIG is administered in for treatment. High-dose steriods were administered in case of repeated IVIG resistance. Prognosis is related with the presence of CAAs (11,13). We aimed to evaluate the patients who had the diagnosis and treated for KD at our center in our center.

METHODS

Patients who were treated for KD between 2012-2022 with the diagnosis of KD were evaluated in our study. Forty-five patients were included in the study. The study was performed retrospectively from their archieve folders. The duration of fever, presence of diagnostic, and additional findings were recorded. Echocardiographic findings were obtained from the archieve folders and hospital systems.

Echocardiographic Evaluation

All the patients included in the study were evaluated for the suspicion of KD at diagnosis. Cardiac functions, appearance and diameters of coronary arteries were examined for diagnosis. Coronary artery lesions were classified as perivascular echogenity, ectasia/dilatation, and aneurysm (14,15). Coronary arteries were grouped according to the AHA 2017 Guidelines. Z-score <2 was classified as normal; Z-score 2-2.5 or if initially <2 and a decrease in Z-score during follow-up ≥1 was classified as dilatation; Z-score 2.5-5 was classified as small aneurysm, Z-score 5-10 was classified as moderate, Z-score ≥10 was classified as large or giant aneurysm (16).

Laboratory Findings

Laboratory findings including erythrocyte sedimentation rate, CRP, white blood cells (WBC), Hgb, PLT, electrolytes (Na, K), and liver functions [aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin] were used for evaluating the patients.

Statistical Analysis

Statistical analyses were performed on NCSS 11 (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA). Frequency and percentage were used for categorical variables. Mean, standard deviation, median, minimum, and maximum values were used for continuous variables. The normal distribution of continuous variables was evaluated using the Shapiro-Wilks test. Non-normally distributed variables were compared using the Mann-Whitney U test for two independent groups. Fisher's Exact test and Fisher Freeman Halton test were used for categorical variables as required. The findings were in 95% confidance interval. P-values <0.05 were regarded as statistically significant.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022-20-08, date: 17.10.2022) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from thethe patients.

RESULTS

Patients in the study revealed 28 male patients and 17 women patients. Male/female ratio was 1.64. Age of the patients was 3.16±2.76 years with a median of 2 years. Patients <1 years old were 9 patients, 1-5 years old were 27 and >5 years old were 9 patients. The age and gender of the patients between the groups in terms of coronary artery involvement and IVIG resistance were similar. There were 34 patients with complete KD and 11 patients with incomplete KD. Complete and incomplete KD were similar in terms of coronary artery involvement and IVIG resistance. Changes in the periferik extremities were present in 64.4%, polymorphic rash was present in 75.6%, conjoctival changes were present in 82.2%, changes in oral mucosa and lips in 82.2%, and lymphadenopathy in 42.2% of the patients. These findings did not show differences in terms of coronary artery involvement and IVIG resistance between the groups. WBC, PLT, AST, ALT, Hgb, and albumin did not differ between the patients with and without coronary artery involvement and IVIG resistance (p>0.05, for all). Coronary involvement was present in 20% of the patients. IVIG resistance was present in 17.8% of the patients (p>0.05) (Table 1).

When the patients were evaluated in terms of coronary artery involvement and IVIG administration time, IVIG administration time was similar between the patients with and without coronary artery involvement. IVIG was administered on the 7.8th day of the illness, and this time was similar in the patients with and without coronary artery involvement. A second dose of IVIG was administered on the mean 9.38th day to 8 patients who were IVIG resistant. This time period was similar to the patients without coronary artery involvement, whereas it was the 12th day in the patients with coronary artery involvement (p>0.05, for all) (Table 2).

Table 1. Sociodemographic findings, principal findings and additional findings according to the presence of coronary artery involvement

		Total (n=45) n (%)	Coronary artery involvement (-) (n=36) n (%)	Coronary artery involvement (+) (n=9) n (%)	p-value	IVIG responders (n=37) n (%)	IVIG resistants (n=8) n (%)	p-value
Gender	Male	28 (62.2)	21 (58.3)	7 (77.8)	[a]0.447	23 (62.2)	5 (62.5)	[a]1.000
	Female	17 (37.8)	15 (41.7)	2 (22.2)		14 (37.8)	3 (37.5)	
Age	Median (min-max)	2 (0.4-11)	2.2 (0.4-11)	1.8 (0.5-6.6)	[b]0.626	2.0 (0.5-10.8)	2.2 (0.4-11)	[b]0.755
	≤1 age	9 (100)	7 (77.8)	2 (22.2)	[aa]0.883	8 (88.9)	1 (11.1)	[aa]1.000
	1-5 age	27 (100)	21 (77.8)	6 (22.2)		22 (81.5)	5 (18.5)	
	≥5 age	9 (100)	8 (88.9)	1 (11.1)		7 (77.8)	2 (22.2)	
Complete/incomplete		34/11	29/7	5/4	[a]0.190	28/9	6/2	[a]1.000
Changes in peripheric extremities (+)		29 (64.4)	25 (69.4)	4 (44.4)	[a]0.245	25 (69.4)	4 (44.4)	[a]0.245
Polymorphic rash (+)		34 (75.6)	29 (80.6)	5 (55.6)	[a]0.190	26 (70.3)	8 (100)	[a]0.169
Conjoctival changes (+)		37 (82.2)	30 (83.3)	7 (77.8)	[a]0.651	32 (86.5)	5 (62.5)	[a]0.137
Changes in oral mucosa and lips (+)		37 (82.2)	32 (88.9)	5 (55.6)	[a]0.039*	29 (78.4)	8 (100)	[a]0.316
LAP (+)		19 (42.2)	16 (44.4)	3 (33.3)	0.712	15 (40.5)	4 (50.0)	0.704
Enduration of BCG (+)		6 (13.3)	6 (16.7)	0 (0)	[a]0.323	5 (13.5)	1 (12.5)	[a]1.000
Perineal desquamation (+)		5 (11.1)	4 (11.1)	1 (11.1)	[a]1.000	2 (5.4)	3 (37.5)	[a]0.033*
Sterile pyuria (+)		3 (6.7)	3 (8.3)	0 (0)	[a]1.000	2 (5.4)	1 (12.5)	[a]0.452
Albumin (g/dL)		3.3 (2-4.3)	3.1 (2-4.3)	3.4 (2.6-4)	[b]0.443	2.9 (2.3-4.3)	3.3 (2-4.3)	[b]0.137
ALT (IU/L)		38 (11-555)	34.5 (13-555)	41 (11-173)	[b]0.921	66 (11-555)	38 (11-555)	[b]0.146
AST (IU/L)		42 (16-419)	40.5 (16-419)	43 (21-226)	[b]0.629	57 (21-419)	42 (16-419)	[b]0.186
Hgb (g/dL)		9.9 (7.2-12.7)	9.9 (7.7-11.6)	9.9 (7.2-12.7)	[b]0.909	9.8 (9-11.4)	9.9 (7.2-12.7)	[b]0.552
WBC (x1000)/mm^3		15.6 (9.30-36.4)	15.6 (9.3-32.0)	20.0 (11.2-36.4)	[b]0.294	14.9 (11.4-23.7)	15.6 (9.3-36.4)	[b]0.603
PLT (x1000)/mm^3		454.0 (0.49-1134)	439.0 (120.0-1134)	626.0 (0.49-732)	[b]0.395	393 (202-732)	454 (0.5-1134)	[b]0.533
Na (mEq/L)		135 (130-141)	134 (130-141)	135 (131-138)	[b]0.275	132.5 (130-141)	135 (130-141)	[b]0.183

Hgb: Hemoglobine, LAP: Lymphadenopathy, Na: Sodium, PLT: Platelets, WBC: White blood cells, BCG: Bacillus Calmette-Guérin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, IVIG: Intravenous immunoglobulin, min-max: Minimum-maximum
[a]Fisher Exact test, [aa]Fisher Freeman Halton test, [b]Mann-Whitney U test
*p<0.05

The laboratory parameters for evaluating the risk factors for coronary artery involvement according to the Harada scoring system were similar in terms of coronary artery involvement (p>0.05, for all) (Table 3).

DISCUSSION

KD is an aute, systemic, febrile vasculitis that occurs usually in infancy and is the most common reason for coronary artery disease during childhood (14). KD is more prevalent in male patients (2). Approximately 85% of the patients were <5 years old with an average of 2 years of age (12). Patients in our study revealed a predominance of male patients with a ratio of 1.64 in concordance with the literature. Scott et al. (17) performed a study and declared that the mean age of the patients with KD was 3 years (range 0.2-16 years). The age intervals of the patients in our study was between 0.4-11 years with a median of 2 years. Most of the patients were between 1-5 years of age but also there are 7 patients older than 5 years in our study.

Principal findings occur approximately with a ratio of 80-85% in patients with KD, except lymphadenopathy, which

Table 2. The relationship between IVIG administration time and coronary artery involvement

		Total	Coronary artery involvement		p-value
			(-)	(+)	
IVIG administration time (day)	n	45	36	9	
	Mean ± SD	7.87±2.89	7.53±2.36	9.22±4.35	[b]0.425
2nd IVIG administration	(-)	37 (82.2)	30 (83.3)	7 (77.8)	[a]0.651
	(+)	8 (17.8)	6 (16.7)	2 (22.2)	
2nd IVIG administration time (day)	n	8	6	2	
	Mean ± SD	9.38±2.13	8.5±1.64	12.00±0.00	-

[a]Fisher's Exact test, [b]Mann-Whitney U test. SD: Standard deviation, IVIG: Intravenous immunoglobulin

Table 3. Risk factors for coronary artery involvement according to Harada scoring system

	Total n (%)	Coronary artery involvement (-) n (%)	Coronary artery involvement (+) n (%)	p-value
Sedimentation (mm/h)				
≤30	0	0	0	-
>30	45 (100)	36 (100)	9 (100)	
CRP (mg/L)				
≤30	2 (4.4)	1 (2.8)	1 (11.1)	[a]0.364
>30	43 (95.6)	35 (97.2)	8 (88.9)	
Albumin (g/dL)				
<3	17 (37.8)	15 (41.7)	2 (22.2)	[a]0.447
≥3	28 (62.2)	21 (58.3)	7 (77.8)	
ALT (IU/L)				
<45	26 (57.8)	21 (58.3)	5 (55.6)	[a]1.000
≥45	19 (42.2)	15 (41.7)	4 (44.4)	
AST (IU/L)				
<45	25 (55.6)	20 (55.6)	5 (55.6)	[a]1.000
>45	20 (44.4)	16 (44.4)	4 (44.4)	
Hemoglobin (g/dL)				
≥10	21 (46.7)	17 (47.2)	4 (44.4)	[a]1.000
<10	24 (53.3)	19 (52.8)	5 (55.6)	
WBC (mm^3)				
≤15,000	17 (37.8)	13 (36.1)	4 (44.4)	[a]0.711
>15,000	28 (62.2)	23 (63.9)	5 (55.6)	
PLT (mm^3)				
<450,000	21 (46.7)	18 (50)	3 (33.3)	[a]0.469
≥450,000	24 (53.3)	18 (50)	6 (66.7)	
Na (mEq/L)				
<133	13 (28.9)	12 (33.3)	1 (11.1)	[a]0.249
≥133	32 (71.1)	24 (66.7)	8 (88.9)	

CRP: C-reactive protein, Na: Sodium, PLT: Platelets, WBC: White blood cells, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, [a]Fisher's Exact test

occurs with a ratio of 40-50% in the literature (1). Gündüz et al. (9) stated oral cavity and lip lesions in 89.7%, conjoctival hyperemia in 76.9%, rash in 74.4%, extremity lesions in 61.5%, and lymphadenopathy in 51.3% of the patients. Our patients had these findings in concordance with the literature with the presence of conjoctival hyperemia and oral mucosal changes mostly and lymphadenopathy less frequently. Perineal desquamation, steril pyuria, and enduration of BCG were some of the additional findings in the patients. According to the studies performed, induration of BCG occurred with a ratio of 16.7%, especially in the incomplete KD (18). Incomplete KD prevelance was 19.8% among the patients with KD in Japan (19). The ratio was between 13.6% and 42% in our country (20,21). Patients with incomplete KD were 24% in our study. The ratios were higher in our country from Japan, suggesting that longlasting fever, which was resistant to antipyretics should remind the KD. Inflammatuary parameters, tended to be higher than normal values, and our results were in accordance with these results.

Cardiovascular involvement is the most threatened complication of this disease. The disease is usually self -limited, but approximately 25-30% of them develop coronary artery involvement. Administering a high dose of IVIG combined with aspirin in the acute phase, especially in the first 7-10 days, is thought to decrease the risk of CAA to 3-5% (22). Different studies established coronary artery lesions with a range of 13-33% (9,23,24), while Gündüz et al. (9) stated the coronary artery involvement with a ratio of 56.4%. Coronary artery involvement may change through a wide range from perivascular echogenity to giant CAAs (9,14). An important coronary artery involvement can result with myocardial infarction and sudden death. Cardiovascular involvement includes the involvement of the pericard, myocard, endocard, and coronary arteries. Findings of heart failure, changes in electrocardiography predicting arrhythmias, angina pectoris, myocardial infarction, cardiomegaly, and pericardial effusion can be present (15). Coronary artery involvement were present in 20% of the patients. None of our patients had electrocardiographic changes reflecting myocardit or pericarditis or ischemia. Cardiomegaly was not detected in our patients. Pericardial effusion was present in one patient. Mitral insufficiency was present in one patient. CALs were present in 9 of the patients, including perivascular echogenity in one, coronary artery dilatation in seven, and moderate Coronary artery involvement in two of them.

Early diagnosis and treatment are critical for managing KD to prevent coronary artery lesions. If the treatment begins after 10 days of the illness, the risk increases. There are some risk factors evaluated for CAAs by different scoring systems (10). The Harada scoring system was introduced in 1991 with high sensitivity (83.3%) to predict coronary artery involvement (25). According to the Harada scoring system, when the parameters mentioned below are present, the risk of coronary artery involvement increases. These parameters are: male sex, age <12 months or >8 years, fever duration >10 days, leukocytosis >15,000/mm^3, low Hgb <10 g/dL, thrombocytosis >450,000/mm^3, hypoalbuminemia (<3 g/dL), hyponatremia, persistent fever, or recurrence of fever >36 h after IVIG administration (2,25). Elevation of inflammatory parameters, including sedimentation, CRP, and WBC, are used to detect systemic inflammation and are used to confirm the diagnosis that are not pathognomonic for KD. Laboratory parameters were evaluated in the patients according to Harada scoring system and the parameters did not show difference in terms of coronary artery involvement. is thought to be related to nonosmotic secretion of antidiuretic hormone and increased vascular permeability. Hyponatremia shows a strong negative correlation with inflammatory mediators such as IL-6 and tumor necrosis factor-alpha (26). Thrombocytosis was related to increased thrombopoietin levels induced by inflammation (27). Hypoalbuminemia is the result of vascular leakage caused by inflammation (28). Sodium, albumin and PLT levels were similar between the patients when they were grouped according to the presence of coronary artery involvement and IVIG resistance.

Öztarhan et al. (10) declared that the frequency of coronary artery lesions (CALs) was 17.6% in their study. There was a male predominance in the patients with CAAs and their age was younger than patients without CALs. Also, the patients <1 years had the highest percentage of CAAs then the other ages. The ratios of complete and incomplete KD was similar in terms of the presence of CAAs. Patients had a frequency of 53.3% in the patients with IVIG resistance. Patients also had higher WBC, PLT, and CRP with similar sedimentation, but lower hematocrit and albumin levels in the presence of coronary involvement (10). Yılmazer et al. (11) stated that patients with IVIG resistance are at a higher risk for coronary artery involvement. Türkuçar et al. (14) exhibited a rate of 33% for CALs, which was similar to Turkish studies but higher than Japanese studies. We showed in our study that gender, age, types of KD, and laboratory parameters did not differ between the patients with coronary involvement and not. Patients <1 years of age and the other age groups had similar ratios of coronary artery involvement. The number of patients >5 years was 9 and only one of them had coronary artery involvement and 2 of them had IVIG

resistance. These results may be related to the limited number of patients included in the study. We also declared in our study that changes in the oral mucosa and lips were less frequently present in the patients with coronary artery involvement. This finding was not declared in the literature earlier. Patients with CALs usually have delayed diagnosis and treatment, so this finding could be healed up or the patient may have incomplete findings supported with additional and laboratory findings at presentation. When we examined in detail, we showed that 5 of the 9 patients with coronary artery involvement had changes in the oral mucosa and lips and 2 of them were incomplete forms of KD.

Although the patients were well treated with IVIG and aspirin, 10-15% of the patients need a second dose of IVIG because of recurrent or persistent fever (1,29). Son et al. (30) declared IVIG resistance with a rate of 13%-21%. When there is IVIG resistance, the administration of the second dose of IVIG is suggested (13). After the second dose of IVIG, fever may be prevalent again in 10%, needing further treatment approaches such as corticosteroids, infliximab, anakinra, cyclosporine, plasma exchange, cyclophosphamide, and rituximab (2,13). Risk factors for IVIG resistance are: age younger than 3 months, incomplete KD, early presence of CAA and early administration of IVIG (≤4 days), delayed administration of IVIG, increased sedimentationand PLT levels. (12,30). Öztarhan et al. (10) stated that IVIG resistance was present with an incidence of 12%. The age at diagnosis under 1 years of age had the highest percentage. IVIG-resistant patients had CAA with a ratio of 50%. WBC, CRP, and ALT were higher, sedimentation and PLT were similar, and hematocrit, and Na were lower in the IVIG-resistant group (10). Yılmazer et al. (11) showed in his study the presence of lower albumin but higher CRP and WBC in the IVIG-resistant group. Ashouri et al. (29) also exhibited low albumin and low sodium levels in their study. Also, it is known that the incomplete form is more likely to be IVIG resistant (11). Li et al. (31) and Egami et al. (32) speculated that not only increased PLT levels but also decreased PLT values are risk factors for IVIG resistance because of intravascular consumption, reflecting greater inflammation. Kobayashi et al. (33) suggested that the presence of PLT ≤300,000 mm^3 was a predictor for IVIG resistance. Our patients with IVIG resistance consisted of 17% of the patients. Age distribution, type of KD, and laboratory findings were similar between the IVIG-resistant and IVIG-responsive groups caused by the probabl effect of a limited number of the patients included. Yılmazer et al. (11) declared similar incidences of principal findings in the IVIG responders and non-responder group. Principal findings were similar between the groups in our study like the study by Yılmazer et al. (11). Desquamation of perine is more prevalent in the IVIG-resistant group in our study. There is not a study performed in the literature evaluating additional findings in terms of IVIG resistance. Perineal desquamation is more prevalent at the end of the subacute phase, and these patients are usually not diagnosed until this time who are more likely to have an incomplete form of KD (2,9). Incomplete KD is more related with IVIG resistance according to the studies in the literature (9,11,13). All the patients with perineal desquamation who had IVIG resistance were incomplete form of KD in our study, compatible with the literature.

It is known that there is a relationship with administration time of IVIG and coronary artery involvement. Türkuçar et al. (14) declared that, longer duration of fever and delayed administration of IVIG accompanied with higher CRP were risk factors for IVIG resistance. Also, it is important to treat these patients in the first 7-10 days to prevent CALs. When we evaluate our patients according to this knowledge, we can state that the administration time of the first IVIG did not differ between the groups in terms of coronary artery involvement and it is under 10 days in both of them. Nearly 17% of our patients had IVIG resistance compatible with the literature, and 25% of the patients with IVIG resistance had coronary artery involvement. The administration time of the second IVIG was after 10 days in the group with coronary artery involvement in our study.

All the patients were treated with IVIG and aspirin at anti-inflammatory dosage as it is suggested in the literature. Aspirin treatment is administered with a dose of 30-50 mg/kg/dose (moderate dose) in Japan and 80-100 mg/kg/dose (high dose) in the USA. The difference in dosage is related to the difference in sensitivity to aspirin. There is no clear evidence that any dose of ASA will decrease the development of CAAs. Therefore moderate dose is preferred because of the potential toxicities (2,7). Aspirin dosage was reduced to 3-5 mg/kg/dose after fever was resolved (7). Some clinicians continued anti-inflammatory dose until 14th day of illness (2). IVIG -resistant patients were treated with a second dose of IVIG. Repeated IVIG resistance was usually treated with pulse methylprednisolone (11,12). Lu et al. (13) administered pulse methylprednisolone followed by oral prednisone tapered in one week. We used aspirin with a dose of 80-100 mg/kg, and after fever resolves aspirin dosage was reduced to antiaggregan dose. Repeated IVIG resistance was treated with pulse methylprednisolone in 2 patients in our study.

Patients without CAA were treated with aspirin of 3-5 mg/kg/dose for 6-8 weeks. Patients with moderate-sized CAAs

were treated with aspirin and clopidogrel. Giant CAAs are treated with antiplatelet and anticoagulant agents such as low-molecule weight heparin and warfarin (2,7). CAAs with grade 0 include coronary arteries that do not have the effect of the disease. Grade 1 includes CAAs, which usually show natural regression within 1 year. Grade 2 includes medium-sized CAAs, which show regression within 2 years in more than half of the cases. Grade 3 includes CAAs that may develop stenosis or occlusion in the future even though high-dose anticoagulant and antiaggregan therapy is administered (3). There was not a patient with giant CAA in our study. There were two patients with moderate CAAs who were treated with aspirin and clopidogrel. The other 7 patients with CALs with perivascular echogenity and mild dilatation were treated only with aspirin for two months. Only one of the moderate CAAs persisted for 1 year. The other one does not keep coming to follow-ups, so we do not have the knowledge about the other CAA.

CONCLUSION

KD should be considered in the differential diagnosis of longlasting fever, which cannot be explained with other reasons in children under 5 years of age. Principal findings combined with additional and laboratory findings should be used for diagnose. Changes in the oral mucosa and lips are less frequent in the patients with coronary artery involvement, whereas perineal desquamation is more prevalent among the patients with IVIG resistance. These findings were not been mentioned in the literature previously. Laboratory findings were not predictive for coronary artery involvement and IVIG resistance in our study. All of our patients were treated properly, and there has not been a cardiac sequel during follow-ups. As a result, even though KD can result with severe complications, timely and correct diagnosis and treatment of the disease usually guarantees a good prognosis.

ETHICS

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (decision no: 2022-20-08, date: 17.10.2022) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from the patients and their parents.

Authorship Contributions

Concept: A.M.M., M.B.A., Design: A.M.M., M.B.A., Data Collection or Processing: A.M.M., M.B.A., Analysis or Interpretation: A.M.M., M.B.A., Literature Search: A.M.M., M.B.A., Writing: A.M.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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