CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

DOI: 10.5152/cjms.2016.118

Evaluation of Epidemiological and Clinical Properties of Kawasaki Disease: A Single Center Experience

Sibel Bozabali, Zülal Ülger, Ertürk Levent, Arif Özyürek

Department of Pediatric Cardiology, Ege University School of Medicine, İzmir, Turkey

BACKGROUND
Kawasaki disease (KD) is a self-limiting vasculitis with unknown etiology. The most feared complication is coronary artery aneurysm. This study aimed to evaluate the epidemiological, laboratory, and clinical properties of Turkish patients with Kawasaki disease.

MATERIAL and METHODS
This retrospective study included the patients with KD who were diagnosed according to the American Heart Association guidelines. The demographic, clinical, and laboratory results of patients were obtained from the recordings.

RESULTS
The study included 72 patients with KD. The male/female ratio was 1.4. The mean age of diagnose was 35±26 months. The most frequent clinical finding was oropharyngeal inflammatory changes (n=64, 89%), and the most rare clinical finding was desquamation in the distal parts of the extremities (n=44, 61%). Coronary artery involvement was detected in 33 (46%) patients, which was higher than the other Asian countries but similar to other studies conducted in Turkey. The most frequently affected vessel was the left coronary artery (n=26, 79%). Coronary artery involvement was higher in males than in females ($p<0.05$). The clinical type was incomplete KD in 26 (36%) patients. During the study period, the number of the patients per year increased with every passing year. Throughout the study duration of 14 years, the number of newly diagnosed incomplete KD patients increased year by year, (17 patients (65%) were diagnosed in the last 5 years).

CONCLUSION
The number of patients diagnosed with typical and incomplete KD has been increasing in recent years. Clinicians' awareness regarding KD may be the reason of this increment. Coronary artery disturbances are frequently observed in Turkish population.

Keywords: Kawasaki disease, incomplete Kawasaki disease, coronary artery, vasculitis, Turkey

INTRODUCTION

Kawasaki disease (KD) is a self-limiting vasculitis during the early childhood period and is characterized by fever, nonexudative conjunctivitis, inflammatory changes of oral mucosa, usually unilateral cervical lymphadenopathy and enduration, erythema and desquamation in the distal parts of extremities, and diffuse polymorphic rash. KD was first defined by Tomisaku Kawasaki from Japan in 1967. It is widely observed worldwide but frequent in Asians, particularly in Japanese (1, 2).

KD is usually observed between the ages of 6 months and 5 years, and it is the most frequent cause of acquired heart diseases in developed countries (3). Without treatment, coronary artery aneurysms are observed in 15%–25% of patients and can be the reason for thrombosis, myocardial infarction, and sudden death. Coronary aneurysms can be prevented five-fold by intravenous immunoglobulin (IVIG) therapy (1, 4).

Epidemiological and clinical studies suggest that KD is caused by an infectious agent in children with a genetic predisposition. However, the responsible agent remains to be determined (1, 5-7). Thus, epidemiological studies have become very important to detect ethnic and regional differences. Although KD is not a very common disease in other Asian countries, it is the second most common vasculitis observed in the pediatric age group in Turkey (8). Studies from Turkey reported much more coronary artery disturbance incidences (25%–45%) (9-15) than those from Japan. In the study of Gulhan et al. (9), the coronary artery involvement was reported earlier and more frequent than other Asian countries. The desquamation of extremities was also reported during the early stages of KD in the Turkish population. This high percentage of coronary artery involvement in Turkish patients could be because of the difference in the causative agents or genetic phenotype.

KD is an important reason for cardiac morbidities that can be prevented or decreased by early and appropriate treatment. There are differences in the course and severity of KD because of ethnic and regional differences. Therefore, it

This study was presented at the 15th National Pediatric Cardiology and Cardiovascular Surgery Congress, 13-16 April 2016, Antalya, Turkey.

Correspondence Author: Sibel Bozabali
E-mail: sibelbozabali@gmail.com

Received: 20.07.2016
Accepted: 30.08.2016

is important for all countries to define the clinical and epidemiological properties of their patients with KD. Hence, this retrospective study aimed to demonstrate the epidemiological and clinical properties of patients with KD in the pediatric cardiology department of Ege University Hospital which is a tertiary referral center of the west part of Turkey.

MATERIAL and METHODS

This retrospective study included patients who were diagnosed and treated as KD and who were followed up between September 1999 and March 2013 in the pediatric cardiology department of our university hospital, which is a tertiary center in the west part of Turkey. The study was approved by the Ethics Committee of the University. Informed consents of the parents were obtained during their follow-up visits.

Patients diagnosed with KD according to the clinical criteria defined by the American Heart Association (AHA) (1). Patients having fever for >5 days and having four of five clinical conditions, i.e., oropharyngeal changes, edema or hyperemia of extremities, cervical lymphadenopathy, bilateral nonexudative conjunctivitis, and skin eruptions, were defined as typical KD. Patients who had <4 of these clinical situations with coronary artery disturbances or three of the supportive laboratory findings, including hypoalbuminemia, pyuria, thrombocytosis, anemia, and high transaminase levels, were defined as incomplete KD (IKD).

Patients' demographic properties, such as age at presentation, sex, and season at diagnosis, were obtained from records. Furthermore, details regarding drugs used for treatment and the response to the treatment were collected.

Echocardiography

For echocardiographic evaluation, the GE Vingmed Vivid Pro 7 (GE Vingmed Ultrasound, Horten, Norway) echocardiography device was used. Coronary artery involvement was defined as positive if one of the following three conditions was detected: 1- Dilatation defined as internal lumen diameter was >+2z scores according to AHA, 2- Aneurysm defined according to the Japanese Ministry of Health criteria (localized saccular or fusiform dilatations of coronary arteries with internal diameter >3 mm in children aged <5 years and >4 mm in children aged ≥5 years, or internal diameter of a segment measured ≥1.5 times that of an adjacent segment), 3- Ectasia defined as an increase in the brightness of the vessel wall and lack of tapering with or without a decrease in the left ventricular ejection fraction, mitral regurgitation, or pericardial effusion (1).

Statistical Analysis

The Statistical Package for Social Sciences (SPSS Inc.; Windows, Version 18.0, Chicago, USA) package program was used for statistical analyses. Descriptive statistics were presented as percentages, means, standard deviations, and frequency tables. Qualitative data were reported as frequencies with percentages, while quantitative data were reported as means with standard deviations.

RESULTS

The study included 72 patients with KD, of which 42 (58%) were males. The male/female ratio was 1.4 ($p<0.05$). The youngest patient was 4 months old, whereas the oldest one was 11 years old. The mean age of diagnosis was 35±26 months. The seasons at the diagnosis were as follows: 27 (38%) winter, 19 (26%) spring, 10 (14%) summer, and 16 (22%) autumn (Table 1).

Clinical Findings

Duration of fever till the diagnosis was 9.4±6.4 days. As shown in the Table 1, oropharynx was affected in 64 (89%) patients, whereas maculopapular rash, conjunctivitis, cervical lymphadenopathy and enduration, hyperemia, or desquamation in the distal parts of the extremities were observed in 59 (82%), 52 (82%), 48 (67%), 47 (65%), or 44 (61%) patients, respectively. The most frequent clinical finding was the involvement of oropharynx, whereas the rarest one was changes in extremities such as desquamation.

The clinical type was IKD in 26 (36%) patients. During the study period, the number of new KD patients increased with every passing year. Throughout the study duration of 14 years, the number of newly diagnosed incomplete Kawasaki disease patients increased year by year, (17 patients (65%) were diagnosed in the last 5 years) as shown in Figure 1.

Laboratory Results

In the acute phase of KD, white blood cell (WBC) count was >15000/mm^3 in 32 (44%) patients. The mean WBC count was 15619±5904/mm^3. The thrombocyte count was >450000/mm^3 in 53 (74%) patients at the first week of the disease, and the mean thrombocyte count at the second week of the disease was 539.485±229.567/mm^3. Erythrocyte sedimentation rate (ESR) was

TABLE 1. The epidemiological and clinical properties of patients with Kawasaki disease

Patients with Kawasaki disease, n (%)	72 (100)
Gender, n (%)	
Female	30 (42)
Male	42 (58)
Age at diagnosis (mean±SD, months)	35±26
Season of diagnosis, n (%)	
Winter	27 (38)
Spring	19 (26)
Summer	10 (14)
Autumn	16 (22)
Mean duration of fever (days)	9.4±6.4
Clinical findings in the acute and subacute phase, n (%)	
Oropharyngeal changes	64 (89)
Rash	59 (82)
Conjunctivitis	48 (67)
Lymphadenopathy	47 (65)
Desquamation	44 (61)
Clinical type, n (%)	
Typical	46
Incomplete	26

n: number; SD: Standard deviation

high (>40 mm/h) in 58 (80%) patients, and the mean ESR value was 83.8±30.5 mm/h. C-reactive protein (CRP) levels were high (>5 mg/dL) in 59 (82%) patients, and the mean CRP level was 10.3±7.4 mg/dL. The mean hemoglobin level was 10.4±1.1 mg/dL.

Cardiovascular Complications

Coronary artery involvement was observed in 33 (46%) patients. The most frequently affected vessel was left main coronary artery (n=26, 79%). Right coronary artery involvement was solely observed in one patient, while others had both the right and left coronary artery involvement (Figure 2). Coronary artery involvement was detected as dilatation in 19 (58%), vessel ectasia in nine (27%), and aneurysm in five (15%) of the 33 patients (Table 2).

Kawasaki disease and coronary artery involvement were higher in males than in females ($p<0.05$). Patients with coronary artery lesions were both males (n=22, 67%) and females (n=11, 33%), whereas patients without coronary artery lesions were usually females (n=22, 56%).

Treatment and Follow-up

All patients were received 2-g/kg single dose IVIG and 80 mg/kg acetyl salicylic acid (ASA). Eight (11%) patients whose fever could not be controlled received second dose of IVIG, one of them also needed steroid after the second dose of IVIG. Only one patient received dipyridamole with ASA because of a large aneurysm (8 mm). During the follow-up period, the sizes of the coronary arteries were reversed in 21 (64%) patients. In 11 (33%) patients, the arteries decreased in diameter, but the z scores were still >+2. Only the size of the coronary artery of the patient who received steroid did not change. There were no visible aneurysms on echocardiography in all patients (Table 2).

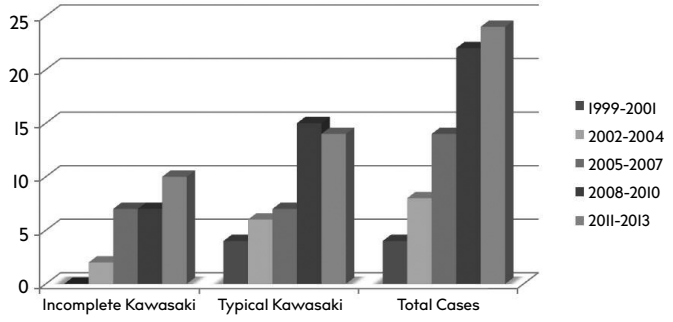

FIGURE 1. Distribution of new patients according to years of diagnose

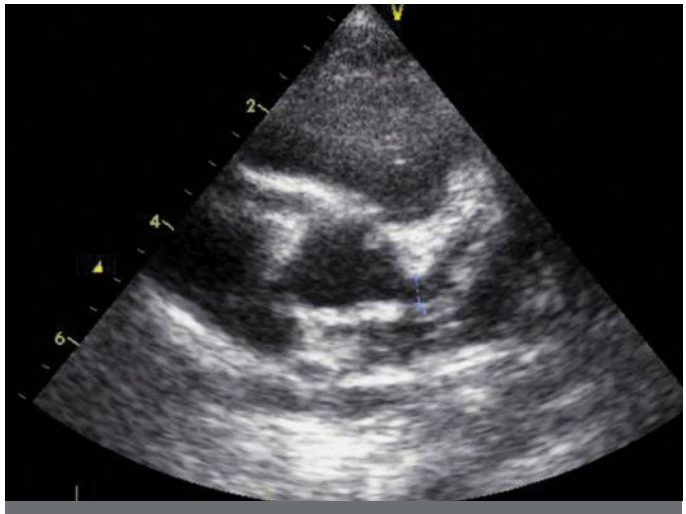

FIGURE 2. Echocardiographic demonstration of the right and left coronary artery dilatation because of Kawasaki disease

DISCUSSION

Kawasaki disease, which is an acute and self-limiting vasculitis during childhood, has become the most important cause of acquired cardiac diseases, particularly in developed countries such as USA and Japan (1, 3). The most feared complication of KD is coronary artery involvement, particularly aneurysms. In our study, the amount of coronary artery involvement was higher than that expected and the number of new KD patients has been increasing in recent years.

Coronary artery involvement was usually reported in up to 25% of diseases in the literature (1, 16-18). In our study, coronary artery disturbances were detected in 46% of patients. When compared with other Asian countries, these high rates were also reported by other studies from Turkey. Coronary artery involvement in Turkish patients with KD is usually reported to be 26%–44% (9-15). This high percentage of coronary artery involvement observed in Turkish patients could be because of the differences in causative agents or genetic variability. KD is more frequently observed in siblings of patients with KD, and genetic factors are considered to have an effect on the occurrence of the disease (1). Therefore, some genetic studies were performed to reveal the genetic predisposition of patients. Tsukahara et al. (19) demonstrated that methylenetetrahydrofolate reductase gene polymorphism has an effect on the development of a coronary artery aneurysm. Onouchi et al. (20) reported that the frequen-

TABLE 2. Distribution of coronary artery lesions at the acute phase, drugs for treatment, and the response to the treatment

Patients with Kawasaki disease, n (%)	72 (100)
Coronary artery involvement, n (%)	
Absent	39 (54)
Present	33 (46)
Dilatation	19 (58)
Ectasia	9 (27)
Aneurysm	5 (15)
Treatment n (%)	
Single dose IVIG+ASA	63 (88)
2 dose IVIG+ASA	7 (10)
2 dose IVIG+single dose steroid+ASA	1 (1)
2 dose IVIG+ASA+Dipiridamol	1 (1)
Coronary artery morbidities, n (%)	
Coronary artery diameter returned to normal z scores	21 (64)
Coronary artery diameter decreased (but still z score >+2)	11 (33)
Dimension of aneurysm not changed	1 (3)
Coronary artery diameter increased or new aneurysm occurred	0 (0)

n: number; IVIG: intravenous immunoglobulin; ASA: acetylsalicylic acid

cy of the allele of rs3741596 in ORAII gene is >20 times higher in Japanese compared with Europeans and alterations have an association with KD. For this reason, more studies are required to explain the probable genetic predisposition in different ethnicities.

Epidemiological studies for KD demonstrate that the KD diagnosis have a seasonal choice and is usually observed during the winter and spring (1). In our study, most patients (64%) were diagnosed in winter and spring, similar to the results of literature worldwide and also those from Turkey (1, 5-7, 9, 15). Viral infections are mostly observed during the winter and spring; therefore, this result of the study supports the idea of an infectious agent in the pathogenesis of KD (5).

The male gender has a tendency for KD and also coronary artery complications (6, 7, 16-18). Similar to previous studies, the male/female ratio was significantly high, particularly in patients with coronary artery involvement, in our study.

Kawasaki disease usually affects small children and its incidence is particularly high between ages of 1 and 2 years. Eighty percent of patients are younger than 4 years, and 50% are younger than 2 years. Patients older than 8 years and younger than 3 months are very rarely observed (16-18). In our study, 85% of patients were diagnosed with KD between ages 1 and 5 years, and the mean age of diagnosis was 35±26 months. The youngest patient was 4 months, whereas the oldest one was 11 years.

When a patient does not have all of the expected clinical findings, KD is defined as IKD (1, 16-18, 21). This condition is mostly observed in very young and very old children. But the laboratory findings resemble the typical ones (6, 7, 22). According to the clinical and laboratory findings, 26 (36%) patients were evaluated as IKD, of which 16 (61%) were younger than 5 months and older than 5 years. These results were similar to those of the literature (21, 22). Jakob et al. (23) study with 315 patients with KD in Germany demonstrated that IKD patients were 1.2-2 years younger than typical KD ones, withthe ratio of IKD patients reported to be 20%. A study from Pakistan reported that the ratio of IKD patients was 18%. However, studies from Turkey reported higher rates of IKD up to 42% like the results of our study (11-13). This result can also be explained by the regional variations of etiological agents or genetic susceptibilities.

Our study demonstrated that with every passing year, the number of new patients with KD and also the IKD forms increased. This result could be due to the increase of the exposure to the etiological agents or most probably increase in the awareness of the clinicians about the disease. In particular, high numbers of IKD forms in the recent years are the signs of an increased awareness of clinicians. However, new studies for identifying the etiology of KD still have a high importance for explanation of this increase in the incidence.

The most frequent clinical finding is the mucocutaneous changes that are observed in >90% of patients with KD (6, 7, 16-18). Similar to the literature, we found that inflammatory changes in the oropharynx of 64 (89%) patients were the most common clinical sign. The rates of other findings were as follows: cutaneous maculopapular rash (82%), conjunctivitis (65%), and desquamation of extremities (61%).

Furusho et al. (24) had used IVIG for the first time in 1984 for treating KD. The incidence of coronary artery involvement without a treatment is 15%–25%, whereas the incidence decreases to 3%–5% with IVIG (6, 7). The mean duration of fever in our study was 9.52±5.47 days, which denoted the delay in the therapy. But according to the knowledge that the effectivity of a treatment in the first 10 days is high, it was considered that the treatment of patients remained effective. Moreover, the follow-up results of the patients in our study demonstrated that 21 of the coronary lesions returned to normal and 11 dilatations decreased in diameter. In other words, the total or partial response rate to the treatment was 96%. There were no visible aneurysms on echocardiography of all patients.

CONCLUSION

In conclusion, the number of patients diagnosed as typical KD and IKD has been increased in recent years. Clinicians' awareness regarding KD may be the reason of this increment. Coronary artery disturbances are frequently observed in the Turkish population, and genetic predisposition may be a reason for it.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University Ethics Committee.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - S.B., A.O.; Design - S.B., Z.U., E.L.; Supervision - S.B., A.O., Z.U.; Resource; Materials; Data Collection and/or Processing - S.B., Z.U., E.L.; Analysis and/or Interpretation - S.B., Z.U., E.L., A.O.; Literature Search - S.B., Z.U., E.L.; Writing - S.B., A.O.; Critical Reviews - S.B., Z.U., E.L., A.O.

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

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

REFERENCES

1. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004; 110: 2747-71. [CrossRef]
2. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi 1967; 16: 178.
3. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. J Pediatr 1991; 119: 279-82. [CrossRef]
4. Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993; 87: 1776-80. [CrossRef]
5. Lloyd AJ, Walker C, Wilkinson M. Kawasaki disease: is it caused by an infectious agent? Br J Biomed Sci 2001; 58: 112-28.
6. Takahashi M, Newburger JW. Kawasaki Disease, In: Allen HD, Driscoll DJ, Shaddy RE, Feltes TF, ed. Moss and Adams' Heart Dis-

ease in Infants, Children, and Adolescents Including the Fetus and Young Adult seventh edition. Philedelphia: Lippincott Williams & Wilkins 2008; I242-56.
7. Newburger J. Kawasaki Disease, In: Andersen RH, Baker EJ, Penny D, Redington AN, Michael LR, Wernowsky G, ed. Paediatric Cardiology third edition. Philedelphia: Churchill Livingstone Elsevier 2010; I067-78. [CrossRef]
8. Ozen S, Bakkaloglu A, Dusunsel R, Soylemezoglu O, Ozaltin F, Poyrazoglu H, et al. Childhood vasculites in Turkey, a nationwide survey. Clin Rheumatol 2007; 26: I96-200.
9. Gulhan B, Kesici S, Beken S, Cilsal E, Kale G, Alehan D, et al. Varying clinical features of Turkish Kawasaki disease patients. Turk J Pediatr 2012; 54: I-6.
10. Beken B, Unal S, Cetin M, Gümrük F. The relationship between hematological findings and coronary artery aneurysm in kawasaki disease. Turk J Haematol 2014; 31: I99-200. [CrossRef]
11. Kayiran SM, Dindar A, Gurakan B. An evaluation of children with Kawasaki disease in Istanbul: a retrospective follow-up study. Clinics (Sao Paulo) 2010; 65: I26I-5. [CrossRef]
12. Aldemir-Kocabaş B, Karbuz A, Karadeniz C, Çiftçi Ö, Özdemir H, Bolkent MG, et al. Another face of Kawasaki disease. Turk J Pediatr 2014; 56: 392-8.
13. Demir F, Karadeniz C, Özdemir R, Yozgat Y, Çelegen K, Karaaslan U, et al. Usefulness of Neutrophil to Lymphocyte Ratio in Prediction of Coronary Artery Lesions in Patients with Kawasaki Disease. Balkan Med J 2015; 32: 37I-6. [CrossRef]
14. Ekici F, Kocabas A, Cetin I. Is there any difference in clinical features of Turkish children with Kawasaki disease? Anatolian J Cardiology 2014; I4: 646-7. [CrossRef]
15. Yılmazer MM, Öner T, Gökalp S, Doksöz O, Güven B, Vupa-Çilengiroğlu O, et al. Risk factors for persistence of coronary artery abnormalities in Turkish children with Kawasaki disease. Turk J Pediatr 2015; 57: 248-53.
16. Burns JC, Glodé MP. Kawasaki syndrome. Lancet 2004; 364: 533-44. [CrossRef]
17. Park MK. Kawasaki Disease. Pediatric Cardiology for Practitioners fifth edition Philedelphia: Mosby Elsevier 2008; 367-76.
18. Burns JC, Kushner HI, Bastian JF, Shike H, Shimizu C, Matsubara T, et al. Kawasaki disease: a brief history. Pediatrics 2000; I06: E27. [CrossRef]
19. Tsukahara H, Hiraoka M, Saito M, Nishida K, Kobata R, Tsuchida S, et al. Methylenetetrahydrofolate reductase polymorphism in Kawasaki disease. Pediatr Int 2000; 42: 236-40. [CrossRef]
20. Onouchi Y, Fukazawa R, Yamamura K, Suzuki H, Kakimoto N, Suenaga T, et al. Variations in ORAI1 Gene Associated with Kawasaki Disease. PLoS One 2016; I1: e0145486. [CrossRef]
21. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Tsuboi S, Aoyama Y, et al. Epidemiplogic features of Kawasaki disease in Japan: results of the 2009-2010 nationwide survey. J Epidemiol 2012; 22: 2I6-2I. [CrossRef]
22. Fulton RR, Newburger JW. Kawasaki Disease, In: Keane JF, Lock JE, Fyler DC, ed. NADAS' Pediatric Cardiology, second edition. Philedelphia: Saunders Elsevier 2006; 40I-4. [CrossRef]
23. Jakob A, Whelan J, Kordecki M, Berner R, Stiller B, Arnold R, et al. Kawasaki Disease in Germany: A Prospective, Population-based Study Adjusted for Underreporting. Pediatr Infect Dis J 2016; 35: I29-34. [CrossRef]
24. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet I984; 2: I055-8. [CrossRef]