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The Relationship Between Kawasaki Syndrome and Viral Infections

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Abstract

Objective: This study aimed to investigate the relationship between Kawasaki syndrome and viral infections.

Methods: The data of the Kawasaki syndrome cases diagnosed between January 2017 to December 2019 were reviewed from hospital records retrospectively.

Results: Among eighteen cases ten were boys, and eight were girls. Their average age at diagnosis was 38.28 ± 28.38 (3-113 months). Seven cases were in winter, eight in spring and autumn, and three in summer diagnosed. The mean length of stay in the hospital was 7.41±3.34 (3-17 days). All patients presented with fever, and the mean duration of fever was 6.94 ± 1.63 days. Six cases were classified as typical KS (33.3%), and twelve as atypical KS (66.7%). Laboratory examinations revealed a leukocyte count of 16507 ± 61817 /mm³, C-reactive protein 8.59 ±5.87 mg/dl, erythrocyte sedimentation rate (ESR) median value 58 mm/hour (18-102). Fourteen patients had cardiac involvement (pericardial effusion, mitral insufficiency), and six had small coronary artery involvement. Both cardiac and coronary artery involvement rates were higher in the atypical KS. In only six cases (33.3%) were the pathogens detected. The detected infectious agents were: Parainfluenza type 4, Parainfluenza type 3, Respiratory syncytial virus, Group A streptococcus, Epstein-Barr virus, Ochrobactrumanthropi, Rubella, Cytomegalovirus.

Conclusion: Detection of infectious agents in only one-third of the cases and the presence of different factors suggest that the Kawasaki syndrome is not related to a specific pathogenic agent. Coronary involvement was not found to be associated with pathogenic agents. However, atypical KS needs more attention for cardiac involvement.

Key words: Kawasaki syndrome, vasculitis, viral infections

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INTRODUCTION

Kawasaki Syndrome (KS) is a systemic vasculitis of childhood that begins acutely, progresses with fever, has an unknown etiology, and is important in terms of complications that could affect small to medium-sized vessels. It occurs especially between the ages of six months and five years and is an important cause of acquired heart diseases in children (1). Approximately 20-25% of untreated patients have coronary artery abnormalities, including an aneurysm, while this rate is less than 5% in patients treated with intravenous immune globulin (IVIG). For this reason, early diagnosis of the disease and timely treatment are extremely important in terms of preventing the development of complications (1-3). The cause of KS has not been fully elucidated. The fact that young children are affected, the fluctuating geographic distribution of the disease, the self-limiting nature of the acute febrile disease, and some epidemiological and clinical features such as enanthema, conjunctival involvement, cervical lymphadenopathy supports that the disease may have an infectious cause (4-7).

In this study, we aimed to investigate the relationship between KS and viral infections. For this reason, medical records were evaluated retrospectively, including demographic data, clinical and laboratory findings of patients who were followed up after discharge at the pediatric cardiology outpatient clinic.

METHODS

A retrospective cross-sectional study was conducted at the University of Health Sciences in the Zeynep Kamil Maternity and Children's Research and Training Hospital, Istanbul, Turkey. This center is one of the largest referral perinatal centers for pregnant women and children in Istanbul. Participants were enrolled from January 2017 to December 2019. The study was approved by the local ethics committee and written informed consent was obtained from the participants' legal guardians (Ethics committee approval: 05.05.2021, 2021/107). The study was performed by the Declaration of Helsinki.

Study Design

Patients who were diagnosed with KS in the pediatric department and followed up at the pediatric cardiology outpatient clinic were included in the study. Parents of all children willing to participate in the study signed informed consent. Detailed clinical history was recorded from the patients' files. The age, gender, time of admission, clinical and laboratory findings, duration of hospital stay, treatments, and short-term complications of the patients were collected, retrospectively. Children with genetic disorders, failed to consent, incomplete clinical laboratory or cardiac examinations were excluded.

The diagnosis of KS was performed according to the presence of four of the five basic findings in addition to fever lasting four days or longer (Table 1). Fever is characteristically high in KS and responds not to antibiotic treatments. Without treatment, fever may continue for about 1-2 weeks and lasted up to 3-4 weeks in affected cases. Patients were classified according to their findings as typical (classical) or atypical (incomplete) KS. Children with persistent fever and less than four characteristic clinical findings were classified as atypical or incomplete KS (8). In the algorithm by McCrindle et al. in 2017 is reported that patients with two or three clinical criteria in addition to fever lasting at least five days and at least three or more accompanying laboratory findings were

classified as atypical KS. Treatment is also recommended if laboratory findings are less than three, and positive findings are detected in the echocardiography (ECHO) examination. These patients also belong to the atypical KS group (9) (Table 1).

The diagnosis of KS in our study was performed according to the KS criteria of the American Heart Academy (9) (Table 1). In addition to American Heart Academy Criteria fever lasting more than four days, patients meeting four or more of five criteria were defined as typical KS. Children who had persistent a fever but had less than four criteria, met three or more supportive laboratory findings, or showed signs of coronary artery involvement by echocardiography were considered as atypical KS and were also treated. As laboratory findings; complete blood count, acute phase reactants like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver and kidney function tests like alanine aminotransferase (ALT), anti-streptolysin O (ASO), sodium (Na), serology of Toxoplasma immunoglobulin M and G, Rubella immunoglobulin M and G, Cytomegalovirus (CMV) immunoglobulin M and G, Parvovirus immunoglobulin M and G, Herpes simplex type1 immunoglobulin M and G, Herpes simplex type2 immunoglobulin M and G, Epstein Barr virus (EBV) viral capsid antigen immunoglobulin M and G, Strep A rapid antigen test, respiratory tract viral panel examination results were recorded.

Cardiac investigation results including transthoracic echocardiography (ECHO), electrocardiographs (ECG) performed by the pediatric cardiology unit of our hospital were noted. Coronary artery diameters were also evaluated in the parasternal short axis. According to the Z-scoring adapted classifications to height and weight of the cases; Large and giant aneurysms were diagnosed if Z-score> 10 absolute size> 8 mm and above, middle aneurysm if Z-score between 5 and 10 (coronary artery diameter <8 mm), small aneurysm if Z-score between 2.5 and 5, Z-score 2 to 2.5. If Z-score <2, and only dilatation is detected no involvement was recorded. Additionally, 1.5 times coronary artery diameter exceeding the adjacent segment was accepted as coronary artery involvement (8,9).

Table 1. Kawasaki syndrome classical diagnostic criteria (8,9).

In addition to the presence of fever for at least four days

1. Changes in hands and feet: In the acute phase, edema in the palm, soles of the feet. In the subacute phase (2nd and 3rd weeks), peeling of the fingers and toes
2. Changes in the lip and oral mucosa: Erythematous and chapped lips, strawberry tongue appearance
3. Bilateral bulbar conjunctivitis
4. Cervical lymphadenopathy (usually unilateral greater than 1.5 cm in diameter)
5. Rash: Polymorph exanthema (non-vesicular and non-bullous)

Laboratory findings supporting Kawasaki disease

In the presence of fever lasting longer than four days, if two or three criteria are met, c-reactive protein > 30 mg/L and / or erythrocyte sedimentation rate > 40 mm/h

Those who provide 3 or more of the following laboratory findings are diagnosed with KH (incomplete).

1. Anemia (assessed according to the patient's age)
2. Thrombocytosis (> 450.000 /mm³ after the seventh day)
3. Albumin < 3 g/dL
4. Alanine aminotransferase (ALT) elevation
5. Leukocyte count (WBC) > 15.000 /mm³
6. Leukocyte> 10 /high-power field in urine (in every field at large magnification under a microscope)

Statistical analysis

Data were analyzed using IBM SPSS for Windows (Release 20.0, SPSS Inc, Chicago, IL). Data were tested for normality with the Kolmogorov–

Smirnov test. Qualitative variables are expressed as percentages and frequencies, normally distributed continuous variables as means (standard deviations, SD), and non-normally distributed variables as medians (interquartile range [IQR] p25-p75) according to the Kolmogorov-Smirnov test.

RESULTS

Among eighteen cases ten were boys, and eight were girls. Three patients were excluded because of other reasons. The average age at diagnosis of the study population was 38.28±28.38 months (3-113 months). Seven cases were in winter, eight in spring and autumn, and three in summer diagnosed. The mean length of stay in the hospital was 7.41±3.34 (3-17 days). Of the studied cases, four were over five years and fourteen were under five years old (Table 2). The mean age of the patients at diagnosis was between 38.28 ± 28.38 (3-113 months).

All patients presented with fever. The mean duration time of fever was 6.94 ± 1.63 days. In addition to fever for five days or more, the most common accompanied findings were changes in oropharynx and lips (n=12, 66.6%), and nonpurulent conjunctivitis (n=10, 55,5%) (Table 2). Six cases were classified as typical Kawasaki (33,3%), and twelve as atypical Kawasaki (66,7%). Laboratory examinations revealed a leukocyte count of 16507 ± 61817 /mm³, C-reactive protein 8.59 ± 5.87 mg/dl, erythrocyte sedimentation rate (ESR) median value 58 mm/hour (18-102), platelet count 374176 ± 112.182 /mm³, hemoglobin value 10.7 ± 1.09 gr/dl, sodium value was 134.18±3.15 mg/dl. Hyponatremia was present in 47.3% of cases.

Fourteen patients (n=14, 77.7%) had cardiac involvement (pericardial effusion, mitral insufficiency), and six had small coronary involvement. The cardiac involvement rate was 66.6% (n=4) in typical KS and 83.3% (n=10) in the atypical form. Coronary artery involvement was observed in one (16,6%) patient of typical KS and in five (41,6%) cases of atypical KS.

The pathogen was detected in only six cases (33.3%) in viral studies of the respiratory tract. The detected infectious agents were: Parainfluenza type 4, Parainfluenza type 3, Respiratory syncytial virus, Group A streptococcus, Epstein-Barr virus, Ochrobactrumanthropi, Rubella, Cytomegalovirus. Ochrobactrumanthropi, Rubella and CMV factors were detected together in one case. Other factors detected in individual cases were listed on Table 3. However, coronary artery involvement was not found to be associated with pathogenic agents.

Intravenous immune globulin treatment was used in all cases in the first ten days after diagnosis of KS. Orally acetylsalicylic acid (ASA) with a dosage of 80 mg/kg/day divided into four doses and simultaneously 2 g/kg intravenous immune globulin (IVIG) was administered with intravenous infusion in twelve hours in all cases. Patients were followed closely in terms of side effects during the IVIG infusion period. No IVIG-related side effect was detected. Decrease of fever 48-72 hours after treatment was accepted as clinical treatment response. The dose of ASA was reduced in children to 3-5 mg/kg/day single dose a day after 48 hours of fever-free follow-up and control transthoracic echocardiography. Patients with fever after 48-72 hours despite ASA and IVIG treatments were accepted as unresponsive KS and an additional IVIG treatment was applied in these with a dosage of 2

mg/kg/day. All patients had the standard treatment protocol for KS. Recovery of cardiac involvement was observed in most of cases (83,3%). Nobody needs infliximab or other therapies. No side effects were reported due to IVIG and ASA treatments.

DISCUSSION

Kawasaki syndrome is common in children below five years of age and men gender (10). In our study, four of the cases were above five years of age, and fourteen were under five years. The male/female ratio was 1.25 consistent with the literature. Studies have found increase in the frequency of KS with seasonal changes. The highest incidence in Japan and Korea was detected in January (winter) and July (summer) (10). The highest incidence in Europe was detected in the winter season (11). In our study, the cases were mostly diagnosed in the winter season and the second most frequently seasons were spring and autumn. Because the seasonal variability and clinical findings used in the diagnosis of KS can also be seen in viral infections, it brings to mind the questions that infectious agents may cause KS. However, definite clear results cannot be shown in the studies conducted on the etiological ground.

Table 2. Age, gender, and clinical manifestations of kawasaki syndrome

	n (%)
Kawasaki syndrome cases	18 (100)
Age	
<5 years	14 (77.7)
>5 years	4 (22.2)
Gender	
Female	8 (44.4)
Male	10 (55.5)
Clinical Findings	
Fever	18 (100)
Oropharynx changes and lip findings	12 (66.6)
Nonpurulent conjunctivitis	10 (55.5)
Cervical lymphadenopathy	9 (50)
Rash	8 (44.4)
Limb change	7 (38.8)

Table 3. Infectious agents, case laboratory and echocardiography findings

INFECTION AGENT	**ADMISSION MONTH**	**AGE**	**LEUKOCYTE NUMBER (UNIT / MM3)**	**CRP (MG/DL)**	**HEART ATTACHMENT**
PARAINFLUENZA TYPE4	SEPTEMBER	2.19 MONTHS	9340	6.68	LEFT CORONARY ARTERY EXPANSION
RSV	DECEMBER	9.5 AGE	9870	0.2	MINIMAL PERICARDIAL EFFUSION
PARAINFLUENZA TYPE3	AUGUST	11 MONTHS	10900	8.4	TRIVIAL MITRAL INSUFFICIENCY
GROUP A STREPTOCOCCUS (GAS)	JUNE	3 AGE	23400	15.9	MILD MITRAL INSUFFICIENCY
EBV	MAY	1.11 YEARS	14400	0.32	NORMAL
OCHROBACTRUM ANTHROPI	NOVEMBER	1.1 AGE	25000	2.3	RIGHT CORONARY ARTERY EXPANSION
RUBELLA	NOVEMBER	1.1 AGE	25000	2.3	RIGHT CORONARY ARTERY EXPANSION
CMV	NOVEMBER	1.1 AGE	25000	2.3	RIGHT CORONARY ARTERY EXPANSION

Another reason why an infectious trigger is considered is that the syndrome is rarely seen in babies younger than three months, possibly as a result of antibodies transmitted from the mother, and the syndrome is almost absent in adults due to the development of immunity due to previous encounters

(7). It was stated in a study by Rowley et al. an agent that could stimulate the immune system may cause KS in genetically susceptible individuals (12). This hypothesis constitutes the basis of examining viral respiratory tract panels and viral antigens in blood during hospitalization. The infectious agents detected in the cases in our study were Parainfluenza type 4, Parainfluenza type3, RSV, GAS, EBV, Ochrobactrumanthropi, Rubella, and CMV. While Ochrobactrumanthropi, Rubella, and CMV were identified together in one case. Other agents were detected from individual patients. In a study conducted in 2013, fourteen different viruses were detected in the polymerase chain reaction and serological tests from clinical samples, and it was thought that they could be associated with KS (13). In another study by Kikuta et al. (14) Epstein Barr virus DNA sequences were obtained in 83% of KS patients and 18% of the control group. Although it is thought that viral infections may cause KS in different reports, more researches should be performed to elucidate the cause and relationships of KS with viral infections. An infectious agent which causes excessive inflammation in predisposed children is a widespread hypothesis, but no specific pathogen has been identified yet. The mystery over KS remains (12-14).

The KS has also a geographic and ethnic origin. Asia is the continent in which KS is most commonly reported. Japan has the highest incidence in this region. In a study conducted in 2014, the rate of KS in children under five years of age in Japan is 308 in 100.000 children (15). South Korea takes second place with 199.7 per 100.000 children in the same age range (16). Although there is no clear data, the rate in our country is 9% among all vasculitis diseases (17).

Kawasaki syndrome is a serious disease with acute vasculitis involvement in childhood. Coronary artery aneurysms are reported in 20% of untreated children. Untreated children and can lead to coronary stenosis, myocardial infarction (MI), or sudden death syndrome (18). In our study had 77.7% of patient cardiac involvement (pericardial effusion, mitral insufficiency), and 33.3% had small coronary involvement. The coronary artery involvement rate was a bit higher than in the literature. We speculated that this result might be related to the fact that study patients were recruited from the pediatric cardiology outpatient clinic. The geographic localization of our country may also affect this high incidence. The cardiac involvement rate was 66.6% in typical KS and 83.3% in the atypical form observed. Coronary artery involvement was detected in one (16.6%) patient of typical KS and in five (41.6%) cases of atypical KS. Both cardiac and coronary artery involvement rates were higher in the atypical KS in our study.

Maggio MC et al. reported adenovirus identification in siblings diagnosed with KS and coronary artery aneurysm (19). However, some studies in the literature could not find a relation between coronary artery involvement and viral etiology (20,21). Similar to the literature our study results could not demonstrate a relationship between a specific viral agent and coronary artery involvement.

It has been shown that early diagnosis and treatment with intravenous IVIG and ASA decreases this risk to 5%, but the medium to long-term prognosis of children with KS is still unknown and a research area (18). All patients had in our study the standard treatment protocol for KS. No side effects

due to treatment regimens were reported. Recovery of cardiac involvement was observed in most of the cases (83.3%) in our study. Nobody needs infliximab or other therapies. However, our study had several limitations. The first limitation is the relatively small sample size, the second limitation is the retrospective design, and the missing of long-term follow-up evaluations of children with Kawasaki syndrome.

CONCLUSION

The detection of infectious agents in one-third of the cases and different factors suggest that the Kawasaki syndrome is not related to a specific agent. Both cardiac and coronary artery involvement rates were higher in the atypical KS. Atypical KS needs more attention for cardiac involvement. Further prospective multicenter trials with larger sample sizes are needed to evaluate the relationship between viral infections and KS.

Ethics Committee Approval: Ethics committee approval was received for this study from Zeynep Kamil Maternity and Children Education and Training Hospital Clinical Research Ethics Committee of University of Health Sciences (No:107)

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Author Contributions:
Concept – CYG, NE, NUK; Design CYG, NE, NUK; Literature search CYG, NE, NUK; Data Collection and/or Processing – CYG, NE, NUK; Analysis and/or Interpretation – CYG, NE, NUK; Writing – CYG, NE, NUK

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