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ARAŞTIRMA MAKALESİ

The retrospective evaluation of cases diagnosed with Kawasaki disease

Kawasaki hastalığı tanısı konulan hastaların geriye yönelik değerlendirilmesi

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ABSTRACT

Aim: Kawasaki disease (KD) is an acute febrile disease of childhood with vasculitis. We aimed to evaluate the epidemiological and clinical characteristics of KD cases diagnosed and treated in the Pediatric Clinic of our hospital in the last decade. **Material and Method:** Forty five patients diagnosed with KD and treated between 01 January 2010 and 01 January 2020 was included in the study. The demographic characteristics, clinical and laboratory findings, and treatment processes of the patients were evaluated retrospectively. **Result:** Of the 45 patients 23 (51.2%) were male. The mean age was 35.26 ± 28.16 months. The average duration of fever was 7,16±3.5 day. The patients were most frequently admitted in the spring (31.1%; 14 patients), and winter (31.1%; 14 patients). Twenty two (71.1%) of the patients diagnosed as complete KD, 13 (28.8%) patients were diagnosed as incomplete KD. While coronary involvement was present in 16 patients (35.5%), 29 patients (64.4%) didn't. The mean platelet count was higher in patients with coronary involvement (p=0.006). **Conclusion:**Cardiac involvement was observed at a rate of 35.5%. Platelet levels were higher in those with cardiac involvement. Considering that the platelet level increases in the subacute period in KD, it can be inferred as a result of an increase in cardiac involvement in patients who were admitted to the hospital late. Therefore the awareness of pediatricians about incomplete KD forms should be increased in addition to KD.

Keywords: kawasaki disease; coronary artery; children

ÖZ

Amaç: Kawasaki hastalığı (KH) çocukluk çağında vaskülitle seyreden akut ateşli bir hastalıktır. Son 10 yılda hastanemiz pediatri kliniğinde KH tanısı alan hastaların epidemiyolojik ve klinik özelliklerini değerlendirmeyi amaçladık. **Gereç ve Yöntem:** 01/01/2021-01/01/2020 tarihleri arasında KH tanısı konulan ve tedavi edilen 40 hasta çalışmaya alındı. Hastaların demografik ve klinik özellikleri, laboratuar bulguları ve tedavi süreçleri geriye yönelik değerlendirildi. **Bulgular:** Kırk beş hastadan 23 (51.2%) ü erkekti. Ortalama yaş 35.26±8.16 ay idi. Ortalama ateş süresi 7.16±3.5 gündü. Hastalar daha çok bahar (%31.1, 14 hasta) ve kış aylarında (%31.1, 14 hasta) başvurdu. Yirmi iki hasta (%71.1) komplet KH, 13 hasta ise (%28.8) inkomplet KH tanısı aldı. Koroner tutulum 16 hastada varken (%35.5), 29 unda yoktu (%64.4). Koroner tutulumu olan hastaların ortalama platelet sayısı yüksekti (p=0.006). **Sonuç:** Kardiyak tutulum %35.5 oranında saptandı. Platelet düzeyi kardiyak tutulumu olanlarda daha yüksekti. KH da platelet düzeyinin subakut dönemde arttığı düşünüldüğünde, hastaneye geç başvuran hastalarda kardiyak tutulumda artış sonucu çıkarılabilir. Bu nedenle çocuk hekimlerinin KH'na ek olarak inkomplet KH konusundaki farkındalıkları artırılmalıdır.

Anahtar Kelimeler: kawasaki hastalığı; koroner tutulum; çocuklar

INTRODUCTION

Kawasaki disease (KD), formerly known as mucocutaneous lymphnode syndrome, is an acute febrile disease of childhood with vasculitis (1). Main findings are fever, conjunctivitis, skin and mucous membrane involvement, and cervical lymphadenopathy (2). The cause of the disease is not fully understood yet (1). It is thought to occur as a result of the abnormal inflammatory response of various infectious agents in genetically predisposed individuals (3).

KD involves many medium-sized arteries, mainly coronary artery, and therefore causes significant mortality and morbidity. If untreated, it results in coronary artery disease up to 25%. Therefore, it is important to perform early diagnosis and treatment in a timely and appropriate manner. Genetic factors are thought to play a role in etiology. In recent years, significant associations with KD in the FAM167A-BLK region of the 8p23-p22 chromosome have been observed (1).

The majority of KD is seen in children between 6 months and 4 years old, but it is known that the disease can be seen in younger babies and sometimes in adolescent (3). It is known that the disease can be seen in all ethnic groups, but its frequency has increased in Asian populations (1).

Diagnosis of KD; It is established by the presence of four of the five basic clinical criteria defined in addition to fever lasting at least five days (Table 1) (1). It is known that these criteria are not fully met in 25% of children diagnosed with the disease (4).Since coronary disease development can be observed at a rate of up to 25% in children who do not receive treatment and the rate of cardiac involvement decreases to 4% with treatment, insistent examination and observation for the diagnosis is important in suspicious clinical pictures (3).

Table 1. Clinical criteria of Kawasaki disease

Fever lasting at least 5 days
Presence of at least four out of five clinical signs
Limb changes (erythema / edema on the hands / feet or peeling of the fingers / toes)
Polymorph exanthema
Bulbar conjunctivitis without exudate
Oral cavity and lip changes (erythema, cracked lip, strawberry tongue)
Oral cavity and lip changes (erythema, cracked lip, strawberry tongue, diffuse mucosal involvement in the oropharynx)
Cervical lymphadenopathy (>1.5 cm in diameter)
Exclusion of diseases with similar findings

In the algorithm published by the American Heart Association, developed for cases where classical KD clinical criteria cannot be met; in addition to fever lasting for at least 5 days, if there are 2 or 3 clinical criteria and accompanying 3 or more supportive laboratory findings, it is defined as incomplete KD, and if the laboratory finding is less than three, the criterion is positive in echocardiography (ECHO) is diagnosed as incomplete KD and treatment is recommended (Table 2) (5).

Table 2. American Heart Association laboratory criteria for incomplete forms of Kawasaki disease

Clinical criteria for fever lasting 5 days and at least 2 clinical criteria of Kawasaki disease OR The fever lasted 7 days and the fever could not be explained for other reasons C-reactive protein in patients ≥ 30 mg/L and / or erythrocyte sedimentation rate ≥ 40 mm/ hour;
Meeting at least 3 of the criteria written below -Anemia (by age) - Platelet value being 450.000 after the 7th day of fever - Albumin ≤ 3 g/dL -Alanine aminotransferase height - White sphere ≥ 15.000 / mm^3 -Detection of ≥ 10 leukocytes in each area in urine

In this study, clinical and laboratory findings, and treatment processes of patients who were followed up and treated with a diagnosis of KD in our clinic for the last ten years were evaluated retrospectively.

MATERIAL AND METHODS

Forty five patients diagnosed with KD and treated in the Ondokuz Mayıs University Medical Faculty between 01 January 2010 and 01 January 2020 were included in the study. Patients whose data could not be reached were excluded. Demographic and clinical characteristics, laboratory findings and treatments of the patients were retrospectively recorded. Patients who met at least four of the five diagnostic criteria in addition to fever lasting more than five days were defined as KD (Table 1). Those who do not meet four of the classical clinical criteria of KD, but who have fever and high C-reactive protein (CRP) / erythrocyte sedimentation rate (ESR), meet at least three of the laboratory criteria defined by the American Heart Association (AHA) or who have cardiac involvement were evaluated as incomplete KD (Table 2).

Following the conventional ECHO examination according to the American Echocardiography Association's pediatric ECHO guidelines, the right and left coronary arteries were evaluated in detail in the parasternal short axis position (12).

Patients diagnosed with KD were given intravenous immunoglobulin (IVIG) infusion of 2 g / kg for 12 hours and oral therapy at a dose of Aspirin 80 mg/kg/day. A decrease in fever within 36 hours following the initiation of IVIG therapy was evaluated as an appropriate response to treatment. The Aspirin dose was reduced to the antiaggregant dose according to the clinical and laboratory results during the follow-up of the patients. The duration of the treatment was arranged according to the type and degree of cardiac involvement. Approval was obtained from the ethics committee of Ondokuz Mayıs University Medical Faculty for the study (No:2021/123).

Statistical analyses

SPSS 20.0 for Windows program was used for statistical analysis. Descriptive statistics; number and percentage for categorical variables, mean and standard deviation were conducted. Comparisons of two independent groups of numerical variables were made with Student's t-test. Statistical significance level was accepted as $p < 0.05$.

RESULTS

Of the 45 patients included in the study, 23 (51.2%) were male, 22 (48.8%) were girls. The mean age of the patients at the time of diagnosis was 35.26 ± 28.16 months. 7 patients (15.5%) were under 2 years old and 19 patients (42.2%) were under 5 years old. The average duration of fever was 7,16±3.5 day (Table 3).

The patients were most frequently admitted in the spring (31.1%; 14 patients), and winter (31.1%; 14 patients), followed by autumn (22.2%; 10 patients) and summer (15.5%; 7 patient).

Table 3. The average laboratory values of Kawasaki disease patients

Variable	(mean±standard deviation)
Age (month) 23/22	35.26±28.16
Duration of fever (day)	7.16±3.510
White Blood cell count (cells/uL)	13981±6384
Hemoglobin (g/dL)	10.3±1.1
Neutrophil count (cells/uL)	9429±5671
Lymphocyte count (cells/uL)	3055±2008
Eosinophil count (cells/uL)	468±618
Platelet count ($x10^9/L^3$)	390±239
Urea (mg/dL)	6.6±2.9
Creatinin (mg/dL)	.29±.08
Sodium (mEq/L)	134±3.8
Albumin (g/dL)	3.2±0.5
ALT (U/L)	53±70
AST (U/L)	46±61
ESR (mm/hr)	76±30
CRP (mg/L)	104±84

CRP: C-reactive protein, ESR:erythrocyte sedimentation rate, ALT: Alanine Aminotransferase, AST: Aspartat Aminotransferase,

Twenty patients had leukocytosis (>15000 cells/uL) (44.4%), 5 patients had anemia (<9 g/dL) (11.1%), 12 patients had thrombocytosis (>450 $x10^9/L^3$) (26.6%), 39 patients had high CRP (>5 mg/L) (86.6%), 43 patients had high ESR (>20 mm/hr) (95.5%), 19 patients had hypoalbuminemia (<3.5 g/dL) (42.2%), 16 had elevated Alanine Aminotransferase (ALT), levels

(>40 U/L) (35.5%), 17 patients had elevated Aspartat Aminotransferase (AST) levels (>40 U/L) (37.7%), and 14 patients had elevated eosinophil count (>400 cells/uL) (31.1%).Twenty two (71.1%) of the patients met four of five KD diagnosis criteria and complete KD, while the other 13 (28.8%) patients were diagnosed as incomplete KD. While coronary involvement was present in 16 patients (35.5%), 29 patients (64.4%) didn't (Table 4). Four patients had right coronary artery, 10 patients had left coronary, and 3 patients had both right and left coronary artery involvement.

Table 4. Comparison of laboratory values of patients with and without coronary involvement in Kawasaki disease

	With coronary involvement (n=16) (35.5%)	**Without coronary involvement (n=29) (64.4%)**	**p value**
Age (month) 23/22	87.69±57.6	90.46±53.9	0.87
Duration of fever (day)	8.0±3.7	6.7±3.4	0.26
White Blood cell count (cells/uL)	15475±8189	12977±5114	0.21
Hemoglobin (g/dL)	10.0±0.94	10.4±1.26	0.19
Neutrophil count (cells/uL)	9889±7033	8967±4842	0.61
Lymphocyte count (cells/uL)	3410±1931	2896±2084	0.42
Eosinophil count (cells/uL)	631±843	382±450	0.20
Platelet count ($x10^9/L^3$)	521±299	321±165	**0.006**
Urea (mg/dL)	6.46±3.58	6.74±2.73	0.77
Creatinin (mg/dL)	0.26±0.09	0.30±0.07	0.11
Sodium (mEq/L)	135±3.10	134±3.37	0.16
Albumin (g/dL)	3.1±0.5	3.3±0.5	0.33
ALT (U/L)	37.2±28.8	61.7±86.6	0.28
AST (U/L)	30.2±15.2	54.7±75.6	0.20
ESR (mm/hr)	87.3±19.4	68.9±34.8	0.09
CRP (mg/L)	85.7±87.8	109.0±76.7	0.36

CRP: C-reactive protein, ESR:erythrocyte sedimentation rate, ALT: Alanine Aminotransferase, AST: Aspartat Aminotransferase

When laboratory findings of patients with and without coronary involvement were compared, the mean platelet count was found to be statistically significantly higher in patients with coronary involvement (p=0.006) (Table 4).The mean age of patients with incomplete KD was lower than that of complete KD and was not statistically significant (Table 5).

We compared the laboratory findings of complete and incomplete KD. The mean lymphocyte count was lower but in normal limits in complete KD (p=0.036). The mean eosinophil count was higher in complete KD group (p=0.048) (Table 5). When evaluated in terms of response to treatment, it was observed that all patients responded to first dose of IVIG treatment. No mortality was observed in any of the patients.

DISCUSSION

The disease was first described in 1961 by Dr Tomisaku Kawasaki. The etiology of the disease is unclear, some infectious agents such as Staphylococcus aureus, Streptococcus pyogenes, Epstein-Barr virus, parvovirus B19, adenovirus and coronavirus have been blamed (7). It is mostly self-limited, but sometimes it can lead to serious complications such as coronary arteritis, coronary artery aneurysm, stenosis, thrombosis, aneurysm and myocardial infarction, and death (8). For the diagnosis of KD, the presence of four of the five basic diagnostic criteria in addition to fever lasting more than five days is sufficient. However, there are difficulties in diagnosis in the presence of less than four (two or three) signs in addition to fever. In this case, evaluating the patients with supportive laboratory findings and ECHO imaging increases the probability of diagnosis (9).

KD is more common in infants and males (5). In current study 7 patients (15.5%) were under 2 years old and 19 patients (42.2%) were under 5 years old. Two patients (4.44%) were under 6 months. The male to female ratio was 1.04 (23/22) and was higher in male in accordance with the literature. In the study of Şahin et al. (10), 87.8% of the patients were under 5 years old, 43.9% were under 2 years old, and 58.5% of the patients were male. Being under 6 months old and over 9 years old, male patient, Asian and Pacific island and having Hispanic ethnicity are indicators of poor prognosis in KD patients (11). The youngest patient in this study was 4 months old and this patient was diagnosed with incomplete KD. The incidence of the disease is very low under 3 months and over 8 years old. Demir et al.(12) detected complete KD in a 43-day-old case. Although the mean age of our incomplete KD patients was lower than the complete KD group, no statistically significant difference was found.

Table 5. Comparison of laboratory values of complete and incomplete Kawasaki disease patients

	With coronary involvement (n=16) (35.5%)	Without coronary involvement (n=29) (64.4%)	p value
Age (month) 23/22	96.03±53.8	69.85±53.7	0.88
Duration of fever (day)	7.48±4	6.62±2.3	0.37
White Blood cell count (cells/uL)	14646.67±6339	13196.15±5732	0.70
Hemoglobin (g/dL)	10.4±1.0	10.0±1.2	0.72
Neutrophil count (cells/uL)	9985±5660	8349±5501	0.82
Lymphocyte count (cells/uL)	2613±1594	3852±2432	0.036
Eosinophil count (cells/uL)	572±713	273±297	0.048
Platelet count ($x10^9/L^3$)	427±274	328±131	**0.085**
Urea (mg/dL)	6.42±2.15	6.26±3.12	0.159
Creatinin (mg/dL)	0.27±0.077	0.30±.006	0.479
Sodium (mEq/L)	134.5±3.5	135.2±2.9	0.375
Albumin (g/dL)	3.2±0.4	3.3±0.6	0.268
ALT (U/L)	62.2±25.3	65.2±23.2	0.121
AST (U/L)	68.5±35.3	71.2±34.2	0.22
ESR (mm/hr)	77.1±31.1	70.8±32.9	0.562
CRP (mg/L)	106.8±85.4	74.2±54.2	0.136

CRP: C-reactive protein, ESR:erythrocyte sedimentation rate, ALT: Alanine Aminotransferase,
AST: Aspartat Aminotransferase

The mean fever duration of the patients was 7.16±3.5 day, the duration of fever was longer in patients with coronary involvement, but there was no statistical difference. Similarly, in the study of Topçu et al. (13), the mean duration of fire of those with cardiac involvement was longer, but it was not significant.

There are some studies in which KD is evaluated seasonally. In an epidemiological study conducted in Japan, it was reported that it is most common in winter in all age groups (14). An increase in frequency has also been reported in the United States of America (USA) in the winter and spring months(15). In a recent study from South Korea, it was reported that it is most common in the summer, especially in June and July, and in the winter in December and January (16). In our study, patients were diagnosed most frequently in spring (31.1%) and winter (31.1%).

Some laboratory abnormalities have been reported in KD include leukocytosis (>15000), normochromic normocytic anemia, thrombocytosis (>450), increased CRP, ESH, ALT, AST, ferritin levels and hypoalbuminemia (17). Increased acute phase reactant is an expected finding in KD, which is defined as an abnormal inflammatory response. In present study 39 patients had high CRP (86.6%), 43 patients had high ESR (95.5%) levels. In the study conducted by Ece et al. (18), leukocytosis, high CRP and ESR were found in more than 75% of the patients. Presence of neutrophilia, thrombocytopenia, hyponatremia, elevation of CRP, elevation in transaminases, poor response to IVIG and / or coronary artery lesion can help predict poor prognosis (11).

Coronary involvement was detected in 35.5% of patients in current study. The rate of cardiac involvement in the course of KD has been reported as 25% in the literature and 27.9-58% in studies conducted in our country (19,20). Cardiac involvement rate was found 33.3% in our study. This rate is higher than the classical literature data and is compatible with the data of our country. Three patients less than 6 months and all had coronary involvement. Coronary involvement was present in one of our 2 patients under 6 months. Our patients with coronary involvement, has increased platelet count than the patients without coronary involvement (p=0.006). Laboratory data in our study belong to the time of admission. Platelet count increase in the subacute period in KD, and the increase in coronary involvement in patients with high platelet values can be explained by late admission in our study. Patients with KD with thrombocytosis should be evaluated with echocardiography.

In the literature, thrombocytopenia has been reported as an important risk factor in the development of coronary artery aneurysm, which is one of the most important complications in KD (21). In our study, there were 2 patients with thrombocytopenia and no coronary aneurysm was found in both.

In epidemiological studies conducted in Japan in recent years, the frequency of incomplete KD has been reported to be 19.8% (9). Studies from our country have reported rates between 13.6% and 42% (14). In another study conducted in Japan, incomplete KD was reported in 16.1% of 15,857 cases diagnosed with KD (22). In a recent study in our country

involving 100 children, the frequency of incomplete KD was reported to be 48% (23). In our study, this rate was found to be 33.3% incomplete KD similar to that study. Kara et al. (24) reported that 83.3% of the patients were diagnosed with complete KD and 16.6% of them were diagnosed with incomplete KD.

Although the lymphocyte count is within normal limits, the mean lymphocyte count was lower and the mean eosinophil count was higher in complete KD ($p < 0.05$), while only 2 of the patients with coronary involvement were incomplete KD, 14 of them were complete KD.

Mc Crindle et al. (5) reported that 10-20% of KD were unresponsive to the first IVIG treatment. In our study, IVIG and high dose aspirin treatment were given to all patients at the time of diagnosis. All of our patients responded to the first IVIG treatment. It has been reported that rapid-onset IVIG treatment is highly effective in preventing coronary artery complications (25).

In conclusion KD was more common in males and 42.2% of children were under 5 years old. Cardiac involvement was observed at a rate of 35.5%. Platelet levels were higher in those with cardiac involvement. Considering that platelet level increases in the subacute period in KD, it means that patients with cardiac involvement present to the hospital late. Therefore, in our country, the awareness of pediatricians about incomplete KD forms should be increased in addition to KD.

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Authors contribution: study concepts/ study design or data acquisition or data analysis/interpretation; EAÖ,TAD writing; EAÖ, All authors have read and agreed to the published version of the manuscript.

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