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Retrospective Evaluation of Patients with Kawasaki Disease

Kawasaki Hastalığı Tanılı Olgularımızın Geriye Yönelik Değerlendirilmesi

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Abstract

Objective: Kawasaki disease (KD) is an acute febrile disease of the childhood characterized by vasculitis. The disease is thought to be due to the abnormal inflammatory response caused by various infectious agents in genetically predisposed individuals. It is known that the disease can be seen in all ethnic groups but it is more common in Asian populations. Although there is no recorded data on the incidence of KD in our country, it cannot be considered as a rare disease.

Material and Methods: In this study, demographic characteristics, clinical and laboratory findings, treatment processes, and if any, complications of the cases diagnosed as KD during the last 5 years were retrospectively evaluated.

Results: In the study, 24 patients were enrolled; 13 were males (54.2%), 11 were females (45.8%), and the median age was 25 months (range 8 to 122 months). Patients were diagnosed most frequently in spring (58.3%) and winter (29.2%). The duration of hospitalization was 11.52 ± 4.4 (range 4-23) days. The most common symptoms accompanying fever were oropharyngeal lesions (79.2-19 of patients). It was seen that 16 (66.7%) of the patients were diagnosed as complete KD and 8 (33.3%) of them were diagnosed as incomplete KD. Eighteen (75%) patients responded to intravenous immunoglobulin (IVIG) at the first dose, 6 (25%) patients had fever after 36 hours of IVIG treatment, and thus were given additional IVIG treatment and 1 (4.2%) patient did not respond to IVIG treatments and steroid was started. Eight (33.3%) of the patients were found to have cardiac involvement and 4 of them were still under antiaggregant treatment.

Conclusion: Increasing awareness of incomplete forms of KD and defining incomplete KD diagnostic laboratory criteria have led to an increase in

Öz

Giriş: Kawasaki hastalığı (KH), çocukluk çağının vaskülit ile seyreden akut ateşli bir hastalığıdır. Hastalığın, çeşitli enfeksiyon ajanlarının genetik olarak yatkın bireylerde yarattığı anormal inflamatuvar cevaba bağlı geliştiği düşünülmektedir. Hastalığın tüm etnik gruplarda görülebildiği ancak Asya kıtası kökenli popülasyonlarda daha sık görüldüğü bilinmektedir. Ülkemizde KH insidansına dair kayıtlı veri bulunmamakla birlikte nadir bir hastalık olarak nitelendirilemez.

Gereç ve Yöntemler: Bu çalışmada, kliniğimizde son beş yılda KH tanısıyla takip ve tedavi edilen hastaların demografik özellikleri, klinik ve laboratuvar bulguları, tedavi süreçleri ve varsa gelişen komplikasyonlar geriye dönük olarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen 24 hastanın 13 (%54.2)'ü erkek, 11 (%45.8)'i kız, ortanca yaş 25 ay (aralık 8-122 ay) idi. Hastalar en sık ilkbahar (%58.3) ve kış (%29.2) mevsimlerinde tanı almıştı. Hastanede yatış süresi 11.52 ± 4.4 (aralık 4-23) gündü. Ateşe en sık olarak orofarengeal lezyonlar eşlik etmekteydi (%79.2-19 hasta). Hastaların 16 (%66.7)'sının komplet KH tanısı aldığı ve diğer 8 (%33.3) hastanın ise inkomplet KH tanısı aldığı görüldü. Hastaların 18 (%75)'inin intravenöz immünglobulin (IVIG) tedavisine ilk dozda yanıt verdiği, 6 (%25) hastanın ise IVIG tedavisinin 36. saati sonrasında ateşinin sürdüğü ve ek doz IVIG tedavisine ihtiyaç duyduğu, 1 (%4.2) hastanın ikinci doz IVIG sonrası ateşi devam ettiğinden steroid tedavisi aldığı görüldü. Hastaların 8 (%33.3)'inde kalp tutulumu saptandığı ve izlemde olan dördünün halen antiagregan tedavi almakta olduğu görüldü.

Sonuç: Hastalığın inkomplet tiplerine dair farkındalığın artması ve inkomplet KH tanısı için laboratuvar kriterlerinin tanımlanmış olması,

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the incidence of KD in recent years. It is useful to keep the defined laboratory criteria in mind in order not to overlook the incomplete forms of the disease where classical KD clinical criteria are not met.

Keywords: Kawasaki disease, mucocutaneous lymph node syndrome, Turkey

KH'nin insidansının son yıllarda artmasını sağlamıştır. Klasik KH klinik kriterlerinin karşılanmadığı inkomplet formların gözden kaçırılmaması adına literatürde yer edinen laboratuvar kriterlerinin göz önünde tutulmasında yarar vardır.

Anahtar Kelimeler: Kawasaki hastalığı, mukokütanöz lenf nodu sendromu, Türkiye

Introduction

Kawasaki disease (KD), formerly known as mucocutaneous lymph node syndrome, is a febrile disease of the childhood characterized by vasculitis (1). Although the cause of the disease has not been clarified yet, it is thought to be due to the abnormal inflammatory response caused by various infectious agents in genetically predisposed individuals (1-3). KD can involve coronary arteries and is the leading cause of acquired cardiac disease in developed countries (4).

Vast majority of KD is seen in the pediatric population aged between 6 months and 4 years; however, it is known that it can be seen in younger infants and sometimes in adolescents (2,5-6). While the disease can be encountered in all ethnic groups, its incidence has increased in Asian populations (1). Along with no recorded data on incidence of KD in our country, it cannot be described a rare disease.

KD diagnosis is made with the presence of four out of five essential clinical criteria in addition to fever lasting at least five days (Table 1) (1). It is evident that though clinical criteria have been determined for diagnosis, 25% of the children diagnosed with this disease does not fully meet these criteria (7). Insistent investigation and observation aimed at diagnosis have the utmost importance in suspicious clinical pictures since coronary disease development can be seen at a rate of 25% in children who do not receive treatment and rate of cardiac involvement drops to 4% with treatment (2,4). In an algorithm published by the American Heart Association developed for cases that do not meet classical KD criteria, it is recommended to diagnose as incomplete KD and start treatment accordingly in the presence of two clinical KD criteria along with fever lasting at least five days or in the presence of fever lasting more than seven days without any typical Kawasaki clinical criteria but with at least three laboratory criteria or in cases with positive findings of KD only on echocardiography (ECHO) (Table 2) (4).

Conventional treatment of the disease involves intravenous immunoglobulin (IVIG) infusion and acetylsalicylic acid treatment. IVIG treatment is repeated in 20-40% of the cases since no response is obtained in the first IVIG treatment (IVIG-resistant Kawasaki) (8). Options such as corticosteroids and more rarely cyclophosphamide, plasmapheresis and infliximab exist in the literature in the treatment of cases resistant to IVIG (1).

In this study, demographics, clinical and laboratory findings, and treatment processes of the patients followed and treated with KD diagnosis in our clinical in the past five years were retrospectively evaluated.

Materials and Methods

Adana City Training and Research Hospital 24 patients diagnosed with and treated for KD between June 1st, 2014 and June 1st, 2019 were included into the study. Demographics and clinical features, laboratory findings, treatments given and complications of the patients were retrospectively recorded. Patients meeting at least four of the five diagnostic criteria of KD along with fever lasting more than five days were defined as KD (Table 1). Patients that did not meet four of the classical criteria of KD but had fever and high CRP/erythrocyte sedimentation value and met at least three laboratory criteria defined by the American Heart Association (AHA) or those with heart involvement were considered as incomplete KD (Table 2).

Coronary artery diameter was evaluated by a pediatric cardiologist carrying out a transthoracic echocardiography. On

Table 1. Clinical criteria of Kawasaki disease

Fever lasting at least five days
Presence of at least 4 of the 5 clinical findings - Extremity alterations (erythema/edema of the hands/feet or denudation of hands/feet) - Polymorphic exanthema - Bulbar conjunctivitis without exudation - Alterations in the oral cavity and lips (erythema, chapped lips, strawberry tongue, common mucosal involvement in the oropharynx) - Cervical lymphadenopathy (> 1.5 cm in diameter)
Exclusion of the diseases carrying same findings

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

Fever ≥ 5 days and having ate least 2 clinical KD criteria OR Fever ≥ 7 days and with no other cause of fever CRP: ≥ 30 mg/L and /or erythrocyte sedimentation rate: ≥ 40 mm/hour;
Meeting at least 3 of the following criteria: - Anemia (according to age) - Thrombocyte value as ≥ 450.000 after the 7th day of fever - Albumin ≤ 3 g/dL - Alanine aminotranspherase (ALT) elevation - White blood cell count: ≥ 15.000/mm^3 - ≥ 10 leukocyte detected on every field of the urine
CRP: C-reactive protein.

Table 3. Demographics and clinical data of the cases with Kawasaki disease diagnosis

	Complete Kawasaki	Incomplete Kawasaki	All patients	p
Number of patients Male Females	16 (66.7%) 10 6	8 (33.3%) 3 5	24 13 11	0.39
Mean age of the patients (month)	36.88	34.63	36.13 ± 27.69 (8-122)	0.14
Number of patients with cardiac involvement	5 (31.2%)	3 (37.5%)	8	1

echocardiography, coronary artery dilatation was considered in the event of seeing the coronary artery lumen diameter determined according to body surface area being above 2.5 SD of the normal value, and coronary artery aneurism was established when the dilatation was above 4 mm.

Oral treatment with 2 g/kg IVIG infusion for 12 hour and acetylsalicylic acid (ASA) at a dose of 80 mg/kg/day were started in patients having received KD diagnosis. A decrease in temperature following the first 36 hours of IVIG treatment was evaluated as appropriate response to treatment. Patients without any response in temperature after the 36th hour of treatment were considered resistant cases, and a second dose of IVIG was given. Steroid treatment was started in patients that did not respond to the second dose of IVIG treatment. ASA dose was decreased to antiaggregant dosage according to clinical and laboratory results of the patients followed. Length of treatment period was arranged taking into account the type and degree of cardiac involvement.

Statistical analysis of the study was performed on the "Statistical Package for Social Sciences (SPSS)" version 20 (IBM Corp., Armonk, NY, USA) program. Shapiro Wilk test was used to assess the normal distribution of numerical data, descriptive statistics of parametric values was calculated as mean± standard deviation and that of the non-parametric values as median (minimum-maximum), and categorical data were expressed as percentage (%). Chi-square test was used in the comparison of categoric variables between the groups. Independent t- test was used in the comparison of numerical values between the groups if the hypotheses were ensured and if not, Mann-Whitney U test was used. Significance was set at $p< 0.05$.

Ethics Board Approval was received from Adana City Training and Research Hospital Clinical Research Ethics Board at the meeting numbered 37 and dated 24.07.2019 with decision numbered 502.

Results

Out of the 24 patients included into the study, 13 (54.2%) were males and 11 (45.8%) were females. Patient age at the time of diagnosis was median 25 months (range, 8-122 months). The patients most commonly referred to hospital in spring (58.3%, 18 patients), followed by winter (29.2%, 7 patients), autumn (8.3%, 7 patients) and summer (4.2%, 1 patient). Length of hospital stay was 11.52 ± 4.4 (range, 4-23 days). Basic demographics and clinical data of the patients are given in Table 3.

When physical examination results were considered, the most common finding, apart from fever, was oropharyngeal lesions (79.2%, 19 patients) followed by extremity alterations (75%, 18 patients), rash (70.8%, 17 patients), conjunctivitis (66.7%, 16 patients) and lymphadenomegaly on the neck (54.2%, 13 patients).

Apart from classic KD criteria, sterile pyuria was determined in 5 (20.8%) patients, arthralgia in 4 (16.7%), arthritis in 2 (8.3%) and meningeal irritation in 1 (4.2%), and reactivation was not detected in the BCG vaccination scar of any patient. It was established that 16 (66.7%) of the patients met four of the five KD diagnostic criteria, and the remaining 8 (33.3%) received incomplete KD diagnosis. While only coronary artery dilation without any laboratory findings was detected in one of the patients out of the eight that received incomplete KD diagnosis, two cases showed cardiac involvement and the presence of at least 3 laboratory findings, and the remaining five met at least three of the laboratory criteria.

A statistically significant difference was not confirmed when the complete and incomplete cases were compared in terms of age, sex, season of application, length of stay, presence of lymphadenomegaly on the neck, oropharyngeal involvement, presence of rash, conjunctivitis, extremity involvement, and cardiac involvement (respectively, p= 0.148, p= 0.39, p= 0.33, p= 0.85, p= 0.08, p= 0.29, p= 0.29, p= 0.06, p= 0.29, p= 1).

Laboratory findings of the patients at the time of diagnosis were as follows: white blood cell count: 19.31 ± 6.5 x 10^3/µL, absolute neutrophil count: 13.94 ± 6.6 x 10^3/µL, hemoglobin: 10.05 ± 1.1 g/dL, thrombocyte median value: 511 x 10^3/µL (range, 117-1083), mean erythrocyte sedimentation rate: 70.79 ± 21.7 mm/hour, CRP median: 160 mg/L (range, 21-396), mean serum albumin: 3.2 ± 0.5 g/dL, and median alanine aminotranspherase: (ALT) 38 U/L (range, 5-412).

Table 4. Clinical features of the KD patients with cardiac involvement

Patient no	Sex	Age	Cardiac involvement	Aneurism type	KD clinical type	Recovery	Low dose ASA
1	Female	31 months	1-2 degree MIV Myocarditis involvement		Complete	Full	Terminated
2	Female	69 months	LCA ectasia	Fusiform	Incomplete	No	Continued
3	Male	16 months	1 MIV Myocarditis involvement irregularities in LCA		Complete	Full	Terminated
4	Female	122 months	Systolic dysfunction 1^0-2^0 MIV		Complete	Full	Terminated
5	Male	8 months	LCA aneurism LCA distal	Saccular	Complete	Full	Terminated
6	Male	55 months	RCA aneurism	Fusiform	Incomplete	Partial	Continued
7	Male	16 months	LCA aneurism	Fusiform	Complete	No	Continued
8	Female	16 months	LCA ectasia	Fusiform	Incomplete	No	Continued

MVI: Mitral valve insufficiency, LCA: Left coronary artery, RCA: Right coronary artery, KH: Kawasaki disease, ASA: Acetylsalicylic acid.

Cardiac involvement was seen in 8 (33.3%) patients. Among the patients with cardiac involvement, 3 (12.5%) had coronary artery aneurism, 2 (8.3%) had coronary artery ectasia, 2 (8.3%) had myocarditis involvement and mitral valve insufficiency (MVI), and one had systolic dysfunction and MVI (4.2%). Low dose acetylsalicylic acid treatment was terminated in patients with no coronary involvement 6-8 weeks later. Low dose acetylsalicylic acid treatment was continued until full recovery was achieved in patients with coronary aneurism and ectasia. Table 4 shows the clinical findings of patients with cardiac involvement. Among the eight patients with coronary involvement, four were males and four were females, and a statistically significant difference was not detected (p= 1).

When patients were evaluated in terms of treatment response, it was concluded that 18 (75%) patients responded well to IVIG treatment with the first dosage, and 6 (25%) patients required additional IVIG treatment (resistant cases) for still having fever after the 36th hour of IVIG treatment. Steroid treatment was started in 1 (4.2%) patient since fever continued despite second dose IVIG treatment. No mortality occurred in any patient.

Discussion

Although agents causing KD have not been illuminated yet, clinical features support the presence of an infectious agent in etiology (1). KD was defined in 1967, and although clinical criteria for diagnosis were described, the disease was sometimes observed to have an incomplete course meeting less than four criteria within the years (4,9). It is believed that due to incomplete cases, the disease may be more common than already diagnosed.

Following the rise in the awareness of the different clinical manifestations of the disease, an increase in KD incidence has been demonstrated in various countries. While incidence in children under the age of five in Japan was reported as 218/100.000 for the years 2007-2008, the incidence was reported as 308/100.000 in the year 2014 (10,11). Incidence has been reported between 4.9-15.2-/100.000 in European countries (12-14). The disease was reported in Turkey for the first time in 1976, and increasing number of cases have been presented in the literature ever since. However, there is not an accurate data on the prevalence of KD in Turkey (15).

It is known that KD is seen in children under the age of five at a rate of 80%. Twenty-one (87.5%) of the cases in this study was 5 years of age or under, which was compatible with the literature. KD is known to be more prevalent in males (16). 54.1% of our cases were males. It has been reported that the male sex is a risk factor for coronary artery involvement; however, a difference was not detected between the sexes in our cases of cardiac involvement.

When evaluated in terms of seasonal distribution, the literature reports for the northern hemisphere that KD incidence increases in winter and spring seasons and is seen the least between August and October (17). Twenty-one (87.5%) patients in our study was diagnosed and treated in winter or spring seasons, which was compatible with the literature.

In developed countries at the present time, since it is clear that KD is the most common cause of acquired cardiac disease and that KD can manifest itself with an incomplete clinical picture at a significant rate, early term diagnosis and appropriate treatment are of utmost importance (1). In a study conducted in Japan, incomplete KD has been report-

ed in 16.1% of 15.857 cases receiving KD diagnosis (18). In a recent study from our country including 100 children, incomplete KD incidence has been reported as 48% (19). 33.3% of the cases in our study were incomplete cases, and was higher than the data of Japan but close to that of Turkey. It is evident that incomplete KD can be seen more frequently in infancy (1). Although mean age of our incomplete KD cases was lower than that of the complete cases, a statistically significant difference was not confirmed. Particularly the evaluation of cases suspected of KD in the infancy period by an experienced team on KD can diminish diagnostic delays.

Cardiac involvement in KD has been reported as 25% in the literature and as 27.9-58% in studies conducted in our country (20,21). Cardiac involvement in our study was determined as 33.3%. This rate is higher than the classic literature data but compatible with the data of our country.

It has been reported in the literature that KD is non-responsive to the first IVIG treatment at a rate of 10-20% (4). In our patient group, non-responsiveness to the first IVIG treatment was 25%. Non-responsiveness to the first IVIG treatment has been reported between 25% and 41.8% in our country (19,22). Fever continued in one of our patients following second IVIG treatment, and this patient responded well to steroid treatment. Other alternative treatments in the literature (cyclophosphamide, plasmapheresis, infliximab) were not administered to our patients.

The literature reports that KD can relapse at a rate of 1% (1). One (4.2%) of our cases relapsed one year later, and it was seen that coronary involvement was not present at the second attack and the patient responded well to the standard IVIG treatment.

Conclusion

The most important factors leading to the increase in the incidence of KD recently are the fact that awareness of the disease has risen and criteria of incomplete KD have been defined and accepted. It is beneficial to consider laboratory criteria found in the literature in order not to miss clinical forms where KD clinical criteria are not met. The pediatricians in our country must be more aware of not only KD but also incomplete forms of KD.

Ethics Committe Approval: The study was approved by the Adana City Education and Research Hospital Clinical Research Ethics Committee (Decision number: 502, Date: 24.07.2019).

Informed Consent: Since the study was retrospective, patient consent was not obtained.

Peer-review: Externally peer-reviewed.

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