An observational study on peripheral blood eosinophilia in incomplete Kawasaki disease

Inkomplet Kawasaki hastalığı'nda periferik eozinofili gözlem çalışması

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ABSTRACT

Objective: To investigate the peripheral blood eosinophilia (PBE) in the acute stage of incomplete Kawasaki disease (iKD).
Methods: Twenty-four patients with iKD (median age; 31.5 months, range; 7-88 months) and 25 with complete Kawasaki disease (cKD) (median age; 37 months, range; 9-140 months) were evaluated between 2004 and 2010 from İzmir Dr. Behçet Uz Children's Hospital records retrospectively. We determined the eosinophil counts and rates from the complete blood count in two study groups before the IVIG treatment and 30 febrile age-matched controls and 30 control cases with congenital heart disease (control Group 1 and 2 respectively). Kruskal-Wallis test was performed in detecting the differences of eosinophil rates and counts between four subgroups.
Results: In iKD group, the mean value of eosinophil rates and median value of eosinophil counts were 4.39±2.5% and 377 cells/mm^3, respectively, which did not significantly different with cKD group (mean eosinophil rates; 5.47±4.8% and median eosinophil counts 525 cells/mm^3) ($p>0.05$). The median values of eosinophil cell counts and mean value of eosinophil rates were 220 cell/mm^3 and 2.83±2.65% in the control group 1 and 165 cell/mm^3 and 1.63±1.43% in the control Group 2 respectively, which were statistically significant lower compared to both study groups ($p< 0.001$).
Conclusion: The rate of PBE was found significantly higher in iKD patients compared to the controls. Since the diagnosis of iKD is difficult, unexplained eosinophilia may be helpful in the presence of suggestive clinical findings of KD. *(Anadolu Kardiyol Derg 2012; 12: 160-4)*
Key words: Kawasaki disease, incomplete, eosinophilia

ÖZET

Amaç: İnkomplet Kawasaki hastalığı'nın (iKD) akut evresinde periferik kan eozinofilisinin (PKE) araştırılması amaçlandı.
Yöntemler: Yirmi dört iKD (ortanca yaş; 31.5 ay, yaş aralığı; 7-88 ay) ve 25 komplet Kawasaki Hastalığı (kKD) tanılı hasta (ortanca yaş; 37 ay, yaş aralığı; 9-140 ay), 2004-2010 yılları arasında İzmir Dr. Behçet Uz Çocuk Hastanesi kayıtlarından retrospektif olarak değerlendirildi. Çalışmaya yaş olarak çalışma grubu ile uyumlu, ateşi olan 30 vaka (kontrol 1) ile konjenital kalp hastalıklı 30 vaka (kontrol 2) kontrol grubu olarak dahil edildi ve kontrol, çalışma grupları eozinofil yüzdeleri ve eozinofil hücre sayıları açsısından IVIG tedavisi öncesinde karşılaştırıldı. Kontrol ve çalışma grupları arasındaki eozinofil farklılıklarını saptamada Kruskal-Wallis testi kullanıldı.
Bulgular: İnkomplet Kawasaki hastalarında PKE görülme yüzdesi ve ortalama değeri sırasıyla %66.6 ve 377 hücre/mm^3 iken cKD grubunda ise sırasıyla; %60 ve 525 hücre/mm^3 idi ve iki grup arasında her iki değer açısından da anlamlı fark saptanmadı ($p>0.05$). Eozinofil hücre sayısının ortanca değeri ile eozinofili yüzdesinin ortalama değeri sırasıyla 1. kontrol grubunda 220 hücre/mm^3 ve %2.83±2.65 iken 2.kontrol grubunda ise 165 hücre/mm^3 ve %1.63±1.43 idi, ve bu değerler çalışma grubunda saptananlara göre istatistiksel anlamlı olarak düşüktü ($p<0.001$).
Sonuç: Kontrol grubu ile karşılaştırıldığında iKD hastalarında PKE anlamlı oranda yüksek saptandı. İnkomplet Kawasaki Hastalığı'nın tanısını koymak zor olduğundan KH'yi destekleyici klinik bulgular varlığında açıklanamayan eozinofilinin olması bu konuda yardımcı olabilir.
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Introduction

Kawasaki disease (KD) is an acute systemic vasculitis that was seen predominantly in infants and young children (1). The publications related to incomplete form of the disease has increased in recent years. Since incomplete form of the disease does not contain all clinical signs of KD, it can easily be confused with other infectious diseases (1, 2). Despite the algorithm (1) was constituted by American Heart Association (AHA) for diagnosis of incomplete Kawasaki Disease (iKD), the diagnostic challenges still remain. The algorithm mentioned above was suggested to use the supplementary laboratory findings such as liver enzymes, white blood cell counts (WBC), erythrocyte sedimentation rate (ESR) for the diagnosis of iKD. The development of the new parameters may contribute to resolve the difficulties in the diagnosis of iKD. The pathogenesis of KD includes exaggerated activation of the immune system, including release of pro-inflammatory cytokines and growth factors, activation of endothelial cells and infiltration of coronary arteries by macrophages, CD8+ cytotoxic lymphocytes, and IgA-producing plasma cells (3-5).

However, some authors have already described the presence of eosinophils in coronary microvessel lesions (6, 7) and increased peripheral blood eosinophilia in the acute stage of a complete form of KD (cKD) previously (6).

Despite these, not much information is known about peripheral blood eosinophilia (PBE) in the acute stage of complete and incomplete form of the disease.

The main purpose of this study was to investigate the PBE in the acute stage of iKD. Moreover, we also aimed to investigate the level of eosinophils in patient with coronary involvements at the time before treatment.

Methods

Study design

We reviewed all the cases diagnosed with Kawasaki Disease between the years 2004 to 2010 from the Pediatric Cardiology Department of İzmir Dr. Behçet Uz Children's Hospital records retrospectively. Complete form of KD was diagnosed clinically using the previously published criteria (1). Although the definition of iKD has not been established yet, available definitions of iKD vary according to the guidelines used. In this study, diagnostic criteria for iKD were based on the latest algorithm within the AHA guidelines (1). According to this reference, iKD was considered in cases with unexplained fever for 5 days associated with 2 or 3 of the principal clinical features of KD associated with the presence of at least three supplemental laboratory findings or abnormalities of the coronary arteries by echocardiography. Supplemental laboratory findings that support the diagnosis include albumin <3.0 g/dL, anemia according to age, elevation of alanine aminotransferase (ALT), platelets (after 7 days) >450 000/mm^3, white blood cell count >15 000/mm^3, and urine >10 white blood cells/high-power field (1).

Study population

In this study, 24 patients with the diagnosis of iKD (12 male, 12 female, median age: 31.5 months, range: 7-88 months) and 25 patients with cKD (14 male, 11 female, median age: 37 months, range: 9-140 months) were enrolled. A few patients in whom laboratory data were incomplete or not considered to be incomplete form according to the last AHA guideline were excluded. For comparison of the PBE, 2 control groups of children whose ages and genders were convenient with study groups hospitalized between 2009 and 2010 were included in the study. The first control group consisted of 30 febrile patients (median age, 33.5 months; range, 7 to 108 months) who had been hospitalized for other reasons different from KD (bacterial or viral pneumonia, urinary tract infection, otitis media and pharyngitis). Second control group consisted of 30 patients (median age, 32 months; range, 7 to 109 months) with congenital heart diseases (not operated). All patients had no medical history of allergic disease.

Echocardiography

Coronary artery abnormalities (CAA) were assessed using 2-dimensional echocardiography (Vivid-3, GE-Vingmed Ultrasound AS, Horten, Norway) according to the previously published criteria (1). Measurements were performed from the inner edges of coronary arteries and excluded points of branching. Coronary artery abnormalities were classified as dilatation (or ectasia) and aneurysm (1).

Laboratory data

Eosinophil cell counts and rates in peripheral blood were retrospectively obtained from the complete blood counts (CBC) in 49 KD patients before the IVIG therapy with median 7.0 days of illness and in 60 age-matched control cases. Peripheral blood eosinophilia was defined as more than 3% of the WBC and the upper limit of the normal range was considered as 350 cells/mm^3 as described previously (8). According to this, eosinophilia was classified into three groups: mild (351 to 1500 cells/mm^3), moderate (>1500 to 5000 cells/mm^3), and severe (>5000 cells/mm^3) (9). In addition to the CBC, differential count, serum levels of aspartate aminotransferase, ALT, albumin level, C-reactive protein (CRP), and also ESR were included.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences version 16 (SPSS Inc, Chicago, IL, USA). Quantitative variables were analysed using the Kolmogorov-Smirnov test to assess sample normality. Student's t-test was applied for normal samples, while the Mann-Whitney U test was applied to compare medians of non-normal distributions. The Chi-square test was used for categorical variables. Since the variances of errors are not homogeneous, Kruskal-Wallis test was performed to detect the differences of eosinophil cell counts and rates between four subgroups (two studies and two control groups). Mann-Whitney U test was used for inter-group comparisons of independent variables. A p value <0.05 was considered statistically significant.

Results

Records of the cKD cases have been fully documented while records of 3 patients with iKD may not be fully accessible or did not meet the AHA criteria for iKD. Eventually, 49 patients were included in the study. Twenty-five children who fulfilled the criteria for KD and 24 were incomplete KD. Demographic, clinical, laboratory, echocardiographic features before IVIG treatment presented in Table 1. In the study group, 43% of the patients were under 2 years old with 21% of the patients being under 1 year of age. Although the percentage of patients with iKD under 2 years old was 47%, no statistically significant difference was present when compared to cKD cases (p>0.05).

Peripheric blood eosinophilia and other laboratory findings

In the study group, 16 of 24 patients (66.7%) with iKD and 15 of 25 patients (60%) with cKD had PBE on admission, although no significant differences were detected between complete and incomplete cases (p>0.05) (Table 1). However, only 4 (13%) of the control patients with congenital heart disease and 4 (13%) of the febrile control patients had PBE (Table 2). Eosinophil cell counts and eosinophilia rates were significantly higher in Kawasaki patients when compared to the control groups (p<0.001) (Table 2). In Kawasaki patients, complete cases had much higher eosinophil cell counts and rates compared to incomplete cases although not statistically significant (p>0.05) (Table 1). PBE determined in control patients was classified as mild degree, while in the study group 25 patients had mild, 5 patients had moderate and 1 patient had severe degree of PBE (Table 3). Four of 5 moderate degrees of PBE and 1 severe PBE was detected in patients with cKD. No statistical significance was found between the cKD and iKD groups in terms of supplemental laboratory data including WBC, ALT, albumin level and ESR (data not shown, p>0.05).

Table 1. Baseline clinical characteristics of the study groups

Variables	Complete KD	Incomplete KD	*p
N	25	24	NS
Age, months	37 (9-140)	31.5 (7-88)	NS
Gender, male/female ratio, n	14/11	12/12	NS
Duration of illness at admission, days	7 (3-18)	7.5 (5-18)	NS
CAA, n (%)	7 (28)	6 (25)	NS
ESR, mm/h	80.6±31.3	69.0±36.4	NS
Platelet, mm^3x1000	547.7±206.2	514.9±223.7	NS
PBE, n (%)	15/25 (60)	16/24 (66)	NS
Eosinophil rates, %	5.47±4.8	4.39±2.5	NS
Eosinophil counts, cells/mm^3	525 (65-5696)	377.5 (150-2180)	NS

Data are presented as mean±SD, median (range) and number (percentage)
*unpaired Student's t-test, Mann-Whitney U test and Chi-square test
CAA - coronary artery abnormalities, ESR - erythrocyte sedimentation rate, KD - Kawasaki disease, NS - not significant, PBE - peripheral blood eosinophilia

Coronary artery abnormalities and eosinophilia

The incidence of initial CAA was 25% (6/24) in iKD and 28% (7/25) in cKD cases on before therapy. After treatment, only two patients (one from iKD, the other from cKD groups) suffered from coronary artery aneurysm, both of whom developed giant aneurysm at admission and maintained in the follow-up. Nine of thirteen patients (69%) who developed CAA had markedly elevated eosinophil rates but, this ratio was not significantly different compared to patients who had no CAA (22/36, 61%) (p>0.05). In addition, no significant differences between patients with CAA and without CAA in terms of eosinophil rates (mean value of 5.55±5.54% and 4.72±3.12% respectively; p>0.05) and eosinophil counts (median value of 468 and 382 respectively; p>0.05). Only one patient had severe eosinophilia (percentage of eosinophilia was 20.2% and the count was 5696 cells/mm^3) and this patient fulfilled the KD criteria and had giant aneurysms. In this case, despite the treatment with IVIG twice followed by pulse methylprednisolone treatment (30 mg/kg bolus) no regression in CAA was observed. Clinical status improved following low-dose

Table 2. Eosinophil rates and eosinophil cell counts before therapy in study and control groups

Variables	iKD group	cKD group	Control 1	Control 2	*Chi-square	*p
Age, months	31.5 (7-88)	37(9-140)	32 (7-109)	33.5 (7-108)	1.11	NS
Eosinophil rate, %	4.39±2.5	5.47±4.8	2.83±2.65	1.63±1.43	28.96	<0.001
Eosinophil counts, cells/mm^3	377 (150-2180)	525 (65-5696)	220 (31-1165)	165 (37-627)	27.11	<0.001
PBE. n (%)	16/24 (66.7)	15/25 (60)	4/30 (13)	4/30 (13)	-	<0.001

Data are presented as mean±SD, median (range) and number (percentage)
*Chi-square test and Kruskal-Wallis test
Mann-Whitney U test for between 2 groups comparisons:
Intergroup comparisons for eosinophil cell counts
**p=0.001 for iKD and control group 1 and p<0.001 for iKD and control group 2
†p=0.001 for cKD and control group 1 and p<0.001 for cKD and control group 2
p=0.418 for iKD and cKD groups
Intergroup comparisons for eosinophil rates
**p=0.001 for iKD and control group 1 and p<0.001 for iKD and control group 2
†p=0.032 for cKD and control group 1 and p<0.001 for cKD and control group 2
p=0.936 for iKD and cKD groups
cKD - complete Kawasaki disease, iKD - incomplete Kawasaki disease, NS - not significant, PBE - peripheral blood eosinophilia

Table 3. Distribution of eosinophil cell counts between study and control groups

Groups	Eosinophil cell count				Total, n
	Normal (<350)	Mild (350-1500)	Moderate (1500-5000)	Severe (>5000)	
cKD group, n	10	10	4	1	25
iKD group, n	8	15	1	0	24
Control 1, n	26	4	0	0	30
Control 2, n	26	4	0	0	30

Data are presented as numbers
cKD -complete Kawasaki disease, i - incomplete, KD - Kawasaki

methotrexate. Coronary aneurysm of this case persisted during the three-year follow-up. The iKD case with giant CAA had no eosinophilia and was admitted to the 18th day of the initiation of the disease. In this case, following two consecutive of doses of IVIG, his fever recovered despite the persistence of CAA during the follow-up (9).

Discussion

Our results demonstrated that peripheral blood eosinophils increase in the acute stage of incomplete and as well as complete KD.

Previous studies regarding eosinophilia in KD cases have included cKD cases and to our knowledge this is the first attempt to study eosinophil measurements in iKD patients (6, 10, 11). The etiology of eosinophilia includes a large number of diseases including vasculitis (Churg-Strauss, helminthic infections, atopic diseases, drug ingestion) (8). The exact mechanism of eosinophilia was not clearly understood in KD (10). However, eosinophilia in the acute stage of KD was suggested to be associated with an underlying allergic disease or immune response (6, 10). In our study, mild increase of eosinophil rate and the count was present nearly in more than 80% of the KD patients with PBE and one patient who developed giant CAA had severe eosinophilia (20%). Eosinophilia may be proposed to be harmful due to its proinflammatory effects. Terai et al. (6) in an autopsy study demonstrated that the population of eosinophils was high in the coronary microvessel lesions of KD. Terai et al. (6) also reported that all patients with coronary artery aneurysms developed eosinophilia. In our study, 9 of 13 patients developed PBE and no statistically significant differences were found between patients who developed CAA and patients who did not develop CAA in terms of eosinophil rates and counts.

Despite the development of sciences, the etiology of KD remains yet to be explored. Generalized microvasculitis has been reported to occur throughout the body in the first 10 days of disease (12). Inflammation persists in the walls of medium and large arteries, especially the coronary arteries, characterized by edema, mononuclear cell infiltration (12). In the current study, the rate of eosinophilia was found to be 66.6% and significantly higher in the iKD group compared to the both control groups ($p<0.001$). Additionally, eosinophil accumulation in blood and myocardial tissues in patients with cKD was reported (6). In the first article by Tomisaku Kawasaki defining KD, 22% of patients with KD were reported to be associated with eosinophilia (13). Kuo et al. (10) have recently shown that eosinophils were significantly elevated in KD both the pre and post IVIG treatment period. These data suggested the probable involvement of eosinophils in the pathogenesis of KD, but the presence of only a few studies has limited these suggestions (6, 10, 11). However, eosinophilia in KD was reported to be a bystander of Th2 response, but not an effector of KD in another study of Kuo et al. (11). Furukawa et al. (14) reported that both increased number of CD23-positive B lymphocytes and serum IgE levels were detected during the latter part of the acute stage. Brosius et al. (15) and Matsuoko et al. (16) also reported that the incidence of atopic dermatitis was significantly higher in the KD patients. This information suggests that an agent causing allergic reactions may have a role in the etiology of the KD.

In our study, no statistically significant difference was observed in ratios of eosinophilia in incomplete and complete KD before the treatment. Incomplete KD was diagnosed clinically by fewer than four findings after excluding mimicking disease. In addition to clinical findings, laboratory findings could be helpful in diagnosis. We have observed no significant differences between cKD and iKD by means of both eosinophil rates and counts. Unexplained eosinophilia could be useful in the diagnosis of iKD, in addition to other supplementary laboratory findings, considering the difficulties in the diagnosis.

Study limitations

In this study, the number of iKD cases may be higher than expected, which may be explained as our clinic is a tertiary referral center for pediatric cardiology. It is also suggested that rate of cKD cases are relatively lower, as the majority of cKD cases are being diagnosed and treated in peripheral centers. Because a few patients had insufficient data were excluded, we were unable to include the consecutive patients in the study. Eosinophil cell counts and rates in peripheral blood were retrospectively evaluated from the CBC in this study. The sensitivity in detection of the eosinophilia may arise when the eosinophil counts obtained from the blood smear. Since we obtained the blood samples for CBC at admission immediately, duration from the onset to collecting blood samples was altered. This may be caused changes in CBC parameters. Finally, because the retrospective nature of the study, we could not investigate the other reasons of eosinophilia in KD patients with moderate or severe eosinophilia.

Conclusion

In our study, the blood eosinophil count was significantly higher in both of cKD and iKD cases when compared to the control groups. Large scaled studies about eosinophilia in KD patients should be planned and according to the results of these

studies, and eosinophilia could be added to supplementary laboratory findings. Since the diagnosis of incomplete KD was difficult, unexplained eosinophilia in the presence of suggestive clinical findings, KD should be kept in mind.

Conflict of interest: None declared.

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