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Original Article

The Use of Mean Platelet Volume, Plateletcrit, and N-terminal Brain Natriuretic Peptide as Biomarkers of Coronary Artery Involvement in Atypical Kawasaki Disease

Atipik Kawasaki Hastalığında Koroner Arter Tutulumunun Biyobelirteçleri Olarak Ortalama Trombosit Hacmi, Plateletkrit ve N-terminal Beyin Natriüretik Peptid Kullanımı

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ABSTRACT

Objective: Coronary artery aneurysm and ectasia develop in approximately 15% to 25% of children with untreated Kawasaki disease (KD). Atypical KD has a higher incidence of coronary artery involvement compared to typical KD. Our aim in this study was to identify new markers to support early diagnosis and prevent complications associated with delayed treatment in atypical KD.

Method: The patients' demographic characteristics, presenting complaints, clinical findings, mean platelet volume (MPV), plateletcrit (PCT), and N-terminal brain natriuretic peptide (NT-proBNP) levels were analyzed. Coronary artery abnormalities were evaluated using two-dimensional echocardiography. Results are expressed as mean (± standard deviation).

Results: Sixty children between the ages of 3 and 96 months who were diagnosed with atypical KD were included. Forty consecutive normal children were included as a control group. NT-proBNP, MPV, and PCT values were 381.7 (±272.7) pg/mL, 5.8 (±0.93) fL, and 0.266% (±0.92%) in the patient group and 48.5 (±28.5) pg/mL, 8.29 (±1.12) fL, and 0.227% (±0.78%) in the control group, respectively (p<0.001 for all). In the comparison of atypical KD patients with coronary artery involvement (CAI subgroup) and without (non-CAI subgroup), the NT-proBNP values in these subgroups were 542.9 (±226.8) and 171 (±161.7) pg/mL (p<0.001), MPV values were 5.8 (±0.77) and 6.54 (±0.95) fL (p<0.005), and PCT values were 0.264% (±0.1%) and 0.269% (±0.08%), respectively.

Conclusion: The simultaneous evaluation of MPV, PCT, and NT-proBNP was useful for the diagnosis of atypical KD. NT-proBNP and MPV can be used as markers of CAI in atypical KD.

Keywords: Kawasaki disease, mean platelet volume, plateletcrit, n-terminal brain natriuretic peptide

ÖZ

Amaç: Koroner arter anevrizması ve ektazisi, tedavi edilmemiş Kawasaki hastalığı (KH) olan çocukların yaklaşık %15 ila %25'inde gelişir. Atipik KH, tipik KH'ye kıyasla daha yüksek bir koroner arter tutulumu insidansına sahiptir. Bu çalışmadaki amacımız, atipik KH'de yeni belirteçler belirleyerek erken tanıyı desteklemek ve gecikmiş tedaviye bağlı komplikasyonları önlemektir.

Yöntem: Hastaların demografik özellikleri, başvuru şikayetleri, klinik bulguları, ortalama trombosit hacmi (MPV), plateletkrit (PCT) ve N-terminal beyin natriüretik peptid (NT-proBNP) düzeyleri araştırıldı. Koroner arter anormallikleri iki boyutlu ekokardiyografi kullanılarak değerlendirildi.

Bulgular: Atipik KH tanısı konan 3 ile 96 ay arasında 60 çocuk dahil edildi. Kırk ardışık çocuk kontrol grubu olarak alındı. Ortalama NT-proBNP, MPV ve PCT değerleri hasta grubunda; 381,7 (±272,7) pg/mL, 5,8 (±0,93) fL ve %0,266 (±0,92) iken; kontrol grubunda ve 48,5 (±28,5) pg/mL, 8,29 (±1,12) fL ve %0,227 (±0,78), hepsi için (p<0,001) saptandı. Ayrıca, koroner arter tutulumu (KAT) olan atipik KH hastalarını, koroner arter tutulumu olmayanlar ile karşılaştırdık. Ortalama (standart deviation) NT-proBNP, KAT alt grubunda 542,9 (±226,8) pg/mL ve KAT olmayan alt grupta 171 (±161,7) pg/mL idi (p<0,001). Ortalama MPV, KAT alt grubunda 5,8 (±0,77) fL ve KAT olmayan alt grupta 6,54 (±0,95) fL idi (p<0,005). Ortalama PCT değeri KAT alt grubunda %0,264 (±0,1%) ve KAT olmayan alt grupta %0,269 (±0,08) idi.

Sonuç: MPV, PCT ve NT-proBNP'nin eş zamanlı değerlendirilmesinin atipik KH tanısında faydalı olduğunu gözlemledik. NT-proBNP ve MPV, atipik KH'de koroner arter tutulumunun belirteçleri olarak kullanılabilir.

Anahtar kelimeler: Kawasaki hastalığı, ortalama trombosit hacmi, plateletkrit, n-terminal beyin natriüretik peptid

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INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology that is predominantly seen in infants and children under 5 years of age[1]. KD is believed to be the most common cause of acquired heart disease in developed countries[2]. Coronary artery aneurysm and ectasia develop in approximately 15% to 25% of children with untreated KD[3,4]. Coronary artery involvement (CAI) may progress to ischemic heart disease and lead to sudden cardiac death. The incidence of these complications can be reduced to less than 5% with early diagnosis and treatments such as intravenous immunoglobulin (IVIG), steroids, biological drugs, and acetylsalicylic acid[5].

Diagnosis of KD is based on diagnostic criteria including fever, rash, cervical lymphadenopathy, and findings in the conjunctiva, lip, oral mucosa, and extremities. There is no specific test or pathognomonic clinical feature of KD. Patients who do not meet all of the diagnostic criteria are diagnosed as having atypical KD (15-20%)[3]. Atypical KD has a higher incidence of CAI compared to typical KD[6].

Additional diagnostic markers are needed for cases in which the clinical presentation is inconclusive. Markers utilized at present include the widely used C-reactive protein (CRP) elevation, high erythrocyte sedimentation rate (ESR), hypoalbuminemia, anemia, high alanine aminotransferase (ALT), leukocytosis, thrombocytosis, and pyuria[7].

N-terminal brain natriuretic peptide (NT-proBNP) is secreted into the circulation via the coronary sinus by myocytes and possibly to some degree directly by perimyocardial fibroblasts upon stimulation by ventricular stretching and various neurohormonal factors. There are reports in the literature of NT-proBNP being used as an auxiliary marker in the diagnosis of KD[8-10].

Platelets are generally known for their function in hemostasis and thrombosis, but their role in immune response and inflammation is of growing interest. Platelet indices include mean platelet volume (MPV), which reflects the average size of the platelets, and plateletcrit (PCT), which refers to the ratio of total platelet volume to blood volume. Studies in which MPV and PCT were used as inflammation markers showed that they have prognostic value in coronary artery disease[11].

We chose the KD patient group for this study due to the ongoing diagnostic challenges and the need for auxiliary markers, especially for atypical presentations. Therefore, we planned to determine the value of biochemical markers used for early diagnosis in the diagnosis and follow-up of atypical KD. In addition, we simultaneously investigated the role of MPV, PCT, and NT-proBNP in diagnosis and management as predictors of CAI. Our aim in this study was to support early diagnosis and prevent complications associated with delayed treatment by identifying new markers.

MATERIALS and METHODS

Study Design

Patients who presented to the Ege University Pediatric Emergency Department between January 2015 and December 2017 and were diagnosed with atypical KD were retrospectively included in the study. Ethics committee approval was obtained from the Ege University Faculty of Medicine Scientific Research Ethics Committee (decision no: 18-5/37, date: 08.05.2018).

Patient Selection

Children under the age of 18 years whose clinical presentation in the pediatric emergency department met the criteria for atypical KD were included. Patients with any data missing from their medical records were excluded from the study.

Definitions

Atypical KD was diagnosed according to the American Heart Association criteria[3]. Patients with fever for at least 5 days and 2 or 3 compatible clinical findings (skin rash; cervical lymphadenopathy; conjunctiva, lip, oral mucosa, and extremity findings) but not meeting the typical KD diagnostic criteria were diagnosed as having atypical KD by experienced clinicians based on evaluation of clinical and laboratory findings. Infants ≤6 months of age with KD are more likely to lack the clinical features of KD other than fever and were diagnosed as having atypical KD if echocardiogram was positive.

CAI was diagnosed if the Z-score of the left anterior descending artery or right coronary artery was ≥2.5, a coronary artery aneurysm was observed, or at least 3 other suggestive features were present, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z-scores of 2-2.5 for the left anterior descending coronary artery or right coronary artery on transthoracic echocardiogram (TTE) performed by the same pediatric cardiologist before initiation of IVIG and acetylsalicylic acid therapy[3].

Data Collection and Patient Assessment

The patients' demographic characteristics, admitting complaints, clinical findings, MPV, PCT, red cell distribution width, leukocyte, thrombocyte, neutrophil, and lymphocyte counts, ESR, and CRP and NT-proBNP levels were investigated. Coronary artery abnormalities were evaluated using two-dimensional echocardiography (Vivid E9, GE-Vingmed Ultrasound AS, Horten, Norway). TTE evaluations were done at admission, week 1, and week 2 for all patients and was repeated intermittently thereafter in patients with CAI.

Statistical Analysis

The data were analyzed using SPSS version 22.0 for Windows (IBM Corp, Armonk, NY). Chi-squared tests were used to compare frequencies and Student's t-test was used to compare (parametric) means. The Mann-Whitney U test was used for variables with non-normal distribution. The diagnostic properties of each biomarker (NT-proBNP, MPV, and PCT) were assessed by receiver operating characteristic (ROC) curve analysis. Diagnostic reliability was evaluated based on the area under the ROC curve within 95% confidence intervals. The diagnostic markers were also analyzed in combination, with sensitivity and specificity as the main outcome measures.

RESULTS

Sixty children between the ages of 3 and 96 months who were diagnosed with atypical KD according to the American Heart Association diagnostic criteria in the Ege University Medical Faculty Pediatric Emergency Department were included in this study. In addition, 40 consecutive children of similar age and sex distribution who presented to the emergency department with non-specific chest pain and no signs of cardiac pathology were included as the control group. Children in the control group were evaluated by a pediatric emergency specialist and were found to have no infectious or rheumatological diseases. The patient group included 29 girls (48.3%) and 31 boys (51.7%). The mean age of the patients was 32.4 months (range, 3-96 months) and 15% of them were infants.

Detailed histories indicated that 68% of the patients had been diagnosed with upper respiratory tract infection, 14% with acute tonsillitis, 11% with acute gastroenteritis, and 7% with urinary tract infection before admission. Antibiotics were used by 71.7% before admission. The median duration of fever in the whole group was 7 days (interquartile range: 3). Hemogram and biochemistry parameters of the patients are shown in Table 1.

All patients underwent TTE evaluation by a pediatric cardiologist on the day of admission to the emergency

Table 1. Laboratory findings of the group diagnosed with atypical Kawasaki disease

Parameters	Mean	Minimum	Maximum	SD (±)
ESR (mm/h)	73.63	10	148	30.8
CRP (mg/dL)	8.21	0.4	25	4.9
WBC (/µL)	17,211	1,590	37,560	7,631
ANC (/µL)	11,085	895	27,690	6,011
HTC (%)	31.26	18	40	3.62
Hb (g/L)	10.3	6.5	13	1.23
MCV (fL)	77.78	62	86	4.99
AST (U/L)	53.81	18	607	79
ALT (U/L)	48.96	4	779	110.37
GGT (U/L)	39.13	4	195	47.52
Total bilirubin (mg/dL)	0.6	0.08	5.2	0.71
Direct bilirubin (mg/dL)	0.17	0.01	3	0.42
Albumin (g/dL)	3.17	1.9	4	0.41
Sodium (mEq/L)	135	122	140	2.93
Potassium (mEq/L)	4.34	2.9	5.4	0.59

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood cell, ANC: Absolute neutrophil count, HTC: Hematocrit, Hb: Hemoglobin, MCV: Mean corpuscular volume, AST: Aspartate aminotransferase ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, SD: Standard deviation

department. CAI was detected in 34 patients (56.7%), Z-score of the left anterior descending coronary artery or right coronary artery was ≥2.5 in 16 patients (25%), and giant coronary aneurysm was detected in 1 patient (3.3%). Seventeen patients (28.4%) had at least 3 other suggestive features including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z-scores of 2-2.5 for the left anterior descending coronary artery or right coronary artery. The coronary arteries of 26 patients (43.3%) were evaluated as normal. CAI was significantly more frequent among patients who presented after 7 days and received IVIG treatment later (p<0.001).

The patients received standard treatment with 2 g/kg IVIG by 12-hour infusion and 80-100 mg/kg/day acetylsalicylic acid. After IVIG therapy, fever regressed in all patients. None of the patients were unresponsive to IVIG therapy.

NT-proBNP, MPV, and PCT values at admission were compared between the patients diagnosed with atypical KD and the control group. Mean [standard deviation (SD)] NT-proBNP, MPV, and PCT values were 381.7 (±272.7) pg/mL, 5.8 (±0.93) fL, and 0.266% (±0.92%) in the patient group and 48.5 (±28.5) pg/mL, 8.29 (±1.12) fL, and 0.227% (±0.78%) in the control group, respectively (p<0.001 for all; Table 2).

We also compared atypical KD patients with CAI (CAI subgroup) to those without CAI (non-CAI subgroup). These two subgroups had mean (SD) NT-proBNP values of 542.9 (±226.8) and 171 (±161.7) pg/mL (p<0.001), mean (SD) MPV values of 5.8 (±0.77) and 6.54 (±0.95) fL (p<0.005), and mean (SD) PCT values of 0.264% (±0.1%) and 0.269% (±0.08%) (p=0.82), respectively (Table 3).

A NT-ProBNP cut-off value of 267.5 pg/mL had sensitivity of 91.2% and specificity of 94% for the detection of CAI in patients diagnosed with atypical KD. When the patients were grouped by age, cut-off values for the detection of CAI in atypical KD were determined as 354.9 pg/mL for 0-12 months (sensitivity 75%, specificity 67%); 258 pg/mL for 13-24 months (sensitivity 95%, specificity 94%), 346.5 pg/mL for 25-36 months (sensitivity 86%, specificity 95%), 409 pg/mL for 27-48 months (sensitivity 66.7%, specificity 90%), and 342 pg/mL for 49-60 months (sensitivity 95%, specificity 100%).

DISCUSSION

The risk of CAI is higher in atypical KD than in classic KD[7]. A number of studies previously reported that baseline coronary artery Z-score before primary treatment, young age, prolonged fever, wider dispersion of symptoms, pyuria, and elevated serum CRP were significantly associated with the development of coronary lesions[12-15].

Table 2. Comparison of NT-proBNP, MPV, and PCT values of the patient and control groups

Parameters	Group	n	Mean	SD (±)	p-value
NT-Pro-BNP (pg/mL)	Patient	60	381.7	272.7	<0.001
	Control	40	48.5	28.5	
MPV (fL)	Patient	60	5.8	0.93	<0.001
	Control	40	8.29	1.12	
PCT (%)	Patient	60	0.266	0.92	<0.001
	Control	40	0.227	0.78	

NT-Pro-BNP: N-terminal brain natriuretic peptide, MPV: Mean platelet volume, PCT: Plateletcrit, SD: Standard deviation

Table 3. Comparison of NT-proBNP, MPV, and PCT values of patients with and without coronary artery involvement

Parameters	Group	n	Mean	SD (±)	p
NT-Pro-BNP (pg/mL)	CAI +	34	542.9	226.8	<0.001
	Normal	26	171	161.7	
MPV (fL)	CAI +	34	5.8	0.77	<0.005
	Normal	26	6.54	0.95	
PCT (%)	CAI +	34	0.264	0.1	0.82
	Normal	26	0.269	0.08	

NT-Pro-BNP: N-terminal brain natriuretic peptide, MPV: Mean platelet volume, PCT: Plateletcrit, SD: Standard deviation

Many studies have been conducted to determine NT-proBNP levels in KD. Zheng et al.[16] determined in their meta-analysis that NT-ProBNP can be used as a marker to demonstrate CAI in typical KD. In that meta-analysis, a mean cut-off value of 900 pg/mL was determined for general sensitivity and specificity in patients diagnosed with CAI in typical KD[16]. In another study, proBNP was increased in KD patients who developed CAI, and patients with serum NT-proBNP elevation >1,000 pg/mL had a ~10 times higher risk of CAI than patients with a modest increase[17]. In the present study, in the subgroup of patients with CAI, the mean (SD) NT-proBNP level was 542.9 (±226.8) pg/mL. The higher NT-proBNP level among patients with CAI suggests that this finding may predict severe disease and high risk of CAI. In our study, NT-proBNP was assessed at the time of admission and was useful in diagnosing atypical KD. A high initial NT-proBNP level supports the diagnosis of KD and indicates that CAI may develop in patients above the cut-off value. Atypical KD should be suspected in a patient presenting with fever for more than 5 days if NT-proBNP level evaluated for any reason is found to be high, even without other signs of typical KD.

Identifying age-specific cut-off values is important, especially as the diagnosis algorithms of atypical KD vary according to age. In patients under 1 year of age with fever for 7 days or longer, laboratory tests for KD are performed regardless of the presence or absence of clinical symptoms, whereas atypical KD is suspected in patients over 1 year of age who have fever for longer than 5 days and 2 or 3 clinical signs[7]. Detection of NT-proBNP levels higher than the age-specific cut-off values will inform the decision to refer patients to a pediatric cardiologist.

The cut-off value obtained in this study was lower than those reported in previous studies, which may be related to the fact that all studies evaluated in the meta-analysis were conducted in Asian populations and included patients with typical KD[16]. Our finding of a lower NT-proBNP cut-off in our population compared to children in Asian populations suggests that NT-proBNP levels may vary by race/ethnicity, and may be a first step toward determining race-specific cut-off values.

MPV and PCT are simple and easily obtained hematologic markers to evaluate platelet function. MPV increases when platelet activation and production increase, and is being utilized as a new inflammation marker[18]. MPV and PCT may be useful in addition to other conventional laboratory tests in the diagnosis of KD. Bozlu et al.[19] determined that MPV was significantly lower in incomplete KD patients compared to a control group, as in our study.

Platelets are generally recognized for their role in hemostasis and thrombosis, but their role in immune response and inflammation is also an area of interest for researchers[20]. Previous studies have shown that MPV is a predictor of increased cardiovascular risk[21]. Liu et al.[22] demonstrated in their study that low MPV predicted CAI in KD patients. In the present study, we also found that MPV was a predictor in atypical KD because patients with CAI had significantly lower values. Reduced platelet volume may be due to consumption or isolation of large platelets activated in the vascular system[23]. It has been suggested that increases in factors such as interleukin-6, granulocyte colony stimulating factor, and macrophage colony-stimulating factor during the acute phase of KD may be responsible for the decrease in platelet volume. However, the mechanism underlying the decrease in MPV in KD has not been clearly demonstrated[24].

MPV is an advantageous marker for early diagnosis because it is included in complete blood count analysis and results are obtained rapidly. In cases where other laboratory parameters that take longer to receive results or echocardiography are either not available or cannot be performed in the early period, MPV can be used to initiate treatment and monitor its effect in the early period.

PCT is the ratio of platelet volume to whole blood volume and positively correlates with platelet count and MPV. A meta-analysis showed that PCT is associated with CAI[25]. Similar to previous studies, we found that PCT was decreased in the acute phase of KD, but there was no significant difference in PCT according to the presence of CAI in this study.

In this retrospective study, we determined that NT-ProBNP and PCT values were significantly higher and MPV values were significantly lower in patients diagnosed with atypical KD compared to the control group. Patients with CAI had significantly higher NT-ProBNP level and significantly lower MPV compared to patients without CAI. However, we detected no significant difference in PCT value between patients with and without CAI. This may be attributed to the limited number of patients in our study and its retrospective design.

Study Limitations

There are several limitations to the present study. Firstly, the retrospective design of our study is the most

crucial limitation. Furthermore, the results are based on a single-center experience with a small cohort. Multicenter, prospective studies that include more patients and typical KD should be conducted.

CONCLUSION

We observed that the simultaneous evaluation of NT-proBNP, MPV, and PCT was useful for the diagnosis of atypical KD. Unlike other studies, we evaluated these parameters simultaneously and showed that NT-proBNP and MPV can be used as markers of CAI. Determination of age-specific NT-proBNP cut-off values will be useful in atypical KD, which is difficult to diagnose and can lead to serious complications. The results of this study show that NT-proBNP, MPV, and PCT can be used as early markers of atypical KD in suspected cases in which echocardiography cannot be performed. NT-proBNP and MPV can also be used as early markers of CAI and as parameters suggestive of a more severe disease course.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Faculty of Medicine Scientific Research Ethics Committee (decision no: 18-5/37, date: 08.05.2018).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer reviewed.

Author Contributions

Surgical and Medical Practices: E.D., C.T., E.U.S., Concept: E.D., A.Y., Design: E.D., G.E., E.U.S., Data Collection or Processing: E.D., C.T., G.E., E.U.S., Analysis or Interpretation: E.D., C.T., G.E., E.U.S., Literature Search: E.D., C.T., E.U.S., Writing: E.D., A.Y., E.U.S.

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