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ARAŞTIRMA/RESEARCH

Association between platelet indices and febrile seizures in children

Çocuklarda trombosit belirteçleri ve febril konvülziyon arasındaki ilişki

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Abstract

Purpose: Febrile seizures (FS) are the most common type of seizures in children.The aim of this study was to evaluate the relationship between platelet indices and FS in children.

Materials and Methods: This prospective study included 40 children who presented with FS and 30 controls who presented with febrile illnesses without seizures. Complete blood counts, including platelet count (PC), mean platelet volume (MPV), and platelet distribution width (PDW) from both groups within 1 hour of FS and 1 month later were obtained.

Results: We found that the MPV and PDW within 1 hour of seizure in children with complex FS group was higher than simple FS group while there was no significant difference in MPV and PDW between patients in the simple and complex FS groups at 1 month. The mean PC was not significantly different between simple and complex FS groups; but, we found that the mean PC in the complex FS group was slightly lower than simple FS group.There was a moderate significant positive correlation between MPV and PDW in children with FS while there was a moderate significant negative correlation between PC and MPV, PDW for FS .

Conclusion: Our findings suggest that the increasing platelet turnover in complex FS group causes a slightly decrease in the PC, an significantly increase of MPV and PDW values indicating that these parameters may play an important role in predicting the severity of FS in children at diagnosis.

Key words: Febrile seizure, mean platelet volume, inflamation

Öz

Amaç: Febril konvülziyon çocuklarda en sık görülen nöbet tipidir. Bu çalışmanın amacı çocuklarda trombosit belirteçleri ile febril konvülziyon arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Bu prospektif çalışmada febril konvülziyon ile başvuran 40 hasta ve kontrol grubu olarak nöbetsiz ateşli hastalık ile başvuran 30 hasta alındı. Febril konvülziyon ve ateşli hastalıkla başvuran her iki gruptada 1 saat ve 1 ay sonra trombosit sayısı, ortalama trombosit hacmi(MPV) ve trombosit dağılım genişliğini(PDW) içeren tam kan sayımına bakıldı.

Bulgular: Bu çalışmada 1. saatin sonunda bakılan MPV ve PDW değerlerinin kompleks febril konvülziyon geçiren grupta basit febril konvülziyon geçiren gruba göre daha yüksek olduğunu bulurken 1. ayın sonunda iki grup arasında fark olmadığını bulduk. Ortalama trombosit sayısında basit ve kompleks febril konvülziyon geçiren gruplar arasında belirgin fark yoktu ama kompleks febril konvülziyon geçiren grupta daha düşük olarak bulduk. MPV ve PDW ile febril konvülziyon geçiren grupta orta derecede pozitif korelasyon varken, trombosit sayısı MPV ve PDW ile febril konvülziyon arasında orta derecede negatif korelasyon vardı.

Sonuç: Bulgularımız kompleks febril konvülziyon hasta grubunda artmış trombosit döngüsünün trombosit sayısında düşüklüğe yol açtığını, belirgin olarak artan MPV ve PDW değerlerinin çocuklarda febril konvülziyonun şiddetini tahmin etmede önemli bir rol oynayabileceğini göstermektedir.

Anahtar kelimeler: Febril konvülziyon, ortalama platelet hacmi, inflamasyon.

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INTRODUCTION

Febrile seizures which occur in association with fevers in children, are the most common type of seizures in young children[1]. The International League Against Epilepsy (ILAE) has defined febrile seizures as seizures occurring in childhood after 1 month of age, (usually between 3 months and 6 years of age), associated with a febrile illness, not caused by an infection of the central nervous system, without previous neonatal or unprovoked seizures, and not meeting the criteria for other acute symptomatic seizures[2]. Although most FS are benign, one-third are complex with a prolonged duration, a partial onset or showing focal features during the seizure or recurrent episodes, and associated with a risk of subsequent epilepsy[3,4].

The mean platelet volume (MPV) reflects platelet size and the rate of platelet production in the bone marrow, and it may be used as an indicator of platelet activation and severity of inflammation[5-9]. Another marker of platelet activation is the platelet distribution width (PDW), which reflects the variability in platelet size[10]. There is a growing body of clinical evidence suggesting that platelets play an important role in the inflammatory response[11]. Some studies have reported that a high MPV is associated with a variety of established risk factors, cardio-and cerebro-vascular disorders, and low-grade inflammatory conditions prone to arterial and venous thromboses[12]. In contrast, other studies reported that high-grade inflammatory diseases, such as active rheumatoid arthritis or attacks of familial Mediterranean fever (FMF), present with a low MPV[13,14]. Some clinical and experimental studies suggest that inflammation, which is intrinsic to the fever response, is involved in the generation of FS; however, the association between MPV and FS has previously been reported in only one study involving children[8,15].

The aim of this study was to evaluate the association between platelet indices and FS. This is the first study to investigate PC, MPV and PDW together in patients with FS.

MATERIALS AND METHODS

The study was approved by the Baskent University Institutional Review Board and Ethics Committee (Project no: KA13/28O). Written informed consent was obtained from the parents of all participants. All consecutive febrile children <6 years of age, who were admitted to Pediatric Emergency Department at Baskent University Hospital, Adana Teaching and Medical Research Center, Adana, Turkey, between February 2014 and July 2014 with or without seizures, were eligible to participate. All children were diagnosed using reliable clinical, laboratory, and neuroimaging techniques according to ILAE criteria. Febrile seizures were classified as simple FS, complex FS, and febrile status epilepticus. The exclusion criteria were as follows: infection of the CNS or any confirmed neurological illness; regular blood transfusion; chronic disease; malignancy; hypercholesterolemia; and aspirin, non-steroidal anti-inflammatory drugs, oral anticoagulant, steroid therapy, and children with or without seizure who were admitted to the emergency department 1 hour after the onset of fever. A total of 3002 patients were admitted with febrile illness between these dates. One hundred thirty-one of these patients had febrile seizure. Eighty-four of these 131 patients with FS was admitted within 1 hour of seizure. However, 40 of 84 patients with FS enrolled in study due to the exclusion criteria and refusion of familes. Approximately 28 of families with FS refused to participate. Many of the families of the 2871 febrile children without seizure did not know the time of the onset of the fever. Beside this, 1255 of them was not admitted within 1 hour of fever onset. Therefore, only thirty of 2871 febrile children without seizure enrolled in study due to the exclusion criteria and refusion of families. All of the patients with and without seizure who enrolled in study came to the follow up.

All 40 patients in the FS group underwent a comprehensive clinical evaluation.The febrile illness, duration of seizures, medical histories of the patient and parents, and time of admission to the hospital after the FS or onset of fever were recorded. Hemoglobin (Hb) concentration, white blood cell (WBC) and C-reactive protein (CRP) levels within 1 hour of seizure onset of fever. Platelet count, MPV and PDW were measured from both groups within 1 hour of seizure onset of fever, and 1 month after a seizure or febrile illness.

For the 30 control children, we recorded body temperature at presentation and the underlying illness at the time of presentation. Hemoglobin concentration, WBC, PC, MPV, and PDW were measured within 1 hour of the fever onset and 1 month after the febrile illness.

Testing

Blood samples were obtained from the antecubital vein from all participants with minimal stasis and collected into tubes containing ethylene-diamine-tetra-aceticacid for determination of a CBC within the first hour and 1 month after a seizure attack or febrile period. All blood specimens were analyzed on an Cell-Dyn 3700 autoanalyser.

The PC, MPV and PDW are simple and useful parameters detected in routine CBC parameters. The normal ranges for the PC, MPV and PDW parameters are 150-400 x 103/uL, 7–11 fl and 0–25%, respectively.

The mean MPV, PDW and PC were compared between the FS and control groups within 1 hour and at 1 month after FS or the febrile illness. In the FS group, we compared the mean PC, MPV and PDW within 1 hour of the FS and at 1 month after the FS attack. Similarly, the mean PC, MPV and PDW within 1 hour and at 1 month after the febrile illness were compared in the control group. The mean MPV, PDW and PC between patients in the simple FS and complex FS groups were also compared.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 15.0; IBM, USA). Descriptive statistics were calculated for demographic data. The results were reported as the mean ± standard deviation or as the median and range. For each continuous variable, the normality of the distribution was confirmed using the Kolmogorov-Smirnov test. Results for categorical variables were compared using a chi-square test. The means for Hb, WBC, PC, CRP level, MPV, and PDW were compared using the Mann-Whitney U-test, Student's t-test, or ANOVA. Spearman or Pearson correlation analysis was used to assess the relationships between FS, and PC, MPV, PDW. P-values < 0.05 were considered statistically significant.

RESULTS

Based on these criteria, 40 febrile children with seizures (FS group) and 30 febrile children without seizures who had a similar age distribution (control group) were enrolled. The FS group was comprised of 23 boys and 17 girls with a mean age of 2.1±1.1 years (range, 0.5 – 5.0 years). The control group was comprised of 18 boys and 12 girls with a mean age of 2.4 ± 1.4 years (range, 0.5–6 years). There were no significant differences between the two groups with respect to age or gender ($p > 0.05$). Of the 40 FS patients, 32 (80%) were diagnosed with simple FS, 8 (20%) with complex FS. Mean temperatures of children in the FS group and control groups were 38.6 ± 0.7°C and 38.4 ± 0.8 °C, respectively ($p > 0.05$) (Table 1).

Table 2 summarizes the median Hb, WBC count, and CRP level in the FS and control groups. There were no significant differences between the group means for Hb concentration, WBC count, and CRP level ($p > 0.05$). Table 3 summarizes the mean values and standard deviations of PC, MPVs and PDWs in then FS and control groups. There were no significant differences in the group means for PC, MPV and PDW values between the FS and control groups within 1 hour and at 1 month after FS or febrile illness. In the FS group there were also no significant differences between the group means for MPV and PDW values within 1 hour of FS and 1 month after a FS attack ($p > 0.05$). In the control group, we detected no significant differences between the group means for MPVs and PDWs within 1 hour of the fever onset and 1 month after the febrile illness ($p > 0.05$).

Table 4 summarizes the mean ± standard deviation for PC, MPVs and PDWs with the FS patients according to type of FS. MPVs and PDWs within 1 hour of seizure in children with complex FS significantly higher than simple FS ($p = 0.04$, $p = 0.001$ respectively). But there was no significant difference in PC between simple and complex FS within 1 hour and at 1 month after a FS. There was also no significant difference between the simple and complex FS groups for MPVs and PDWs at 1 month after seizure.

Table 5 summarizes the correlation between mean PC, MPV and PDW value in children with FS. The mean PC count in the simple FS and complex FS groups were not significantly different; however, the mean PC in the complex FS group was lower than in the simple FS group. There was a moderate significant positive correlation ($p < 0.05$) between MPV and PDW in children with FS while there was a moderate significant negative correlation between mean PC and MPV ($r = - 0.40$), PDW ($r = -0.29$) for FS ($p < 0.05$).

Table 1. Demographic and clinical characteristics of the study groups

	FS group (*n*=40)	Control group (*n*=30)
Age in years (range)	2.2±1.1 (0.5–5.5)	2.4±1.4 (0.5–6.0)
Gender (F/M)	23/17	18/12
Body temperature at time of admission (°C)	38.6±0.7	38.4±0.8

FS: febrile seizure; (age and body temperature are reported as the mean ± standard deviation)

Table 2.Comparison of Hb concentration, CRP level and WBC count, between the groups

	FS group(n = 40)			Control group(n = 30)			
	Median	Min	Max	Median	Min	Max	p
WBC (×10)	9650	4500	25400	10850	4500	21800	0.87
Hb (mg/dl)	11.3	7.2	13.6	11.5	8.6	12.9	0.73
CRP((mg/dl)	10.3	1.0	146	12.2	3	197	0.19

Abbreviation: FS, febrile seizure; MPV, mean platelet volume; PDW, platelet distribution width; WBC, white blood cell; PLT, platelet; Hb, hemoglobin; CRP, C-reactive protein

Table 3.. Results (mean ± standard deviation = M ± SD) for Platelet, MPV and PDW at 1 hour and 1 month of admission in the FS patients and controls

	FS groups (n = 40) M±SD	Control groups (n = 30) M±SD	P
Platelet counts at 1 hour after FS	295.475 ± 20.139	308.800 ± 15.924	0.62
Platelet counts at 1 month after FS	336.150 ± 19.282	375.800 ±16.954	0.14
MPV values at 1 hour after FS	6.41 ± 0.74	6.34 ± 0.61	0.68
MPV values at 1 month after FS	6.47 ± 0.89	6.65 ± 0.82	0.41
PDW values at 1 hour after FS	16.93 ± 0.91	17.0 ± 0.77	0.74
PDW values at 1 month after FS	16.98 ± 0.96	17.0 ± 0.62	0.84

Abbreviation: FS, febrile seizure; MPV, mean platelet volume;PDW, platelet distribution width

Table 4. Results for Platelet, MPV and PDW at 1 hour and 1 month of admission in the FS patients

Simple FS group (*n* = 32) X ± SS		Complex FS group (*n* = 8) X ± SS	P
Platelet counts at 1 hour after FS	308.218 ± 23.979	244.500 ± 25463	0.21
Platelet counts at 1 month after FS	339.281 ± 22.563	323.625 ± 36219	0.75
MPV values at 1 hour after FS	6.30 ± 0.67	6.97 ± 0.88	0.04
MPV values at 1 month after FS	6.30 ± 0.79	6.87 ± 1.14	0.08
PDW values at 1 hour after FS	16.7 ± 0.63	17.8 ± 1.3	0.001
PDW values at 1 month after FS	16.89 ± 0.99	17.35 ± 0.73	0.23

Abbreviation: FS, febrile seizure; MPV, mean platelet volume; PDW, platelet distribution width

Table 5. Correlation between mean platelet values, MPV and PDW in children with FS

	r	p
Platelet count-MPV	-0.40	0.0001
Platelet count-PDW	-0.29	0.01
MPV-PDW	0.43	0.0001

Abbreviation: FS, febrile seizure; MPV, mean platelet volume; PDW, platelet distribution width

DISCUSSION

The occurrence of FS in only a sub-group of children with febrile illnesses indicates the importance of host factors and genetic susceptibility. There is a growing body of evidence to suggest that inflammatory cells and pro-inflammatory cytokines play significant roles in the generation of FS[16,17]. It is known that brain inflammation promotes increased neuronal excitability, decreases the seizure

threshold, and is likely to be involved in the molecular, structural, and synaptic changes which characterize epileptogenesis[18]. Previous studies have also revealed increased levels of inflammatory cytokines in the plasma and cerebrospinal fluid of patients with FS[19].

Platelet indices have been shown to be an important component of the inflammatory response and the size of platelet is associated with the intensity of inflammation[12] . The role of MPV as an indicator of platelet function has been investigated in association with several inflammatory disorders, such as cystic fibrosis, ulcerative colitis, rheumatoid arthritis, FMF, and infections[6,10,12,20,21]. In acute exacerbations of chronic obstructive pulmonary disease in which the intensity of inflammation increases, the MPV has been shown to be significantly lower, while the serum leukocyte count and percentage of neutrophils were higher than during the stable period[22]. In support of this observation, some studies have suggested that cytokines, such as IL-3 and IL-6, which play a role in the inflammatory process, may influence megakaryocyte ploidy and lead to the production of larger and more reactive platelets, thus affecting the MPV[22]. The relationship between MPV and infection, especially sepsis, has also been evaluated in a number of studies[23-25]. Robbins et al reported that at least two patterns of platelet size changes are possible in response to infection (an early rise in MPV in severe infections, such as septicemia (may be associated with thrombocytopenia); and a later decrease in MPV with a sustained, chronic, or persistent bacterial infection (may be associated with thrombocytosis)[26]. As reported in the literature, a number of studies have shown that low or high MPV values are associated with acute or chronic inflammatory disorders[8-14,20-23,25,26]. In contrast, the clinical validity and utility of PDW have not been established; however, some authors argue for use of the PDW in inflammatory disorders. Herve et al reported that because the PDW represents the variability in PLT size, the PDW may potentially provide more information than MPV concerning the activity of the number of PLT[10].

MPV values were previously evaluated in only one study involving children with FS; however, the relationship between FS and MPV and PDW has not been evaluated previously[8]. Ozaydin et al speculated that because epilepsy is a brain inflammatory disorder and MPV decreases in inflammatory conditions, MPVs in complex FS should be lower than simple FS[8]. Therefore, Ozaydin et al retrospectively compared MPVs between simple and complex FS and found that MPV was significantly lower in children with complex FS than in the simple FS group. Although the sample size was large, it was a retrospective study. In contrast to Ozaydin et al we found that MPVs and PDWs within 1 hour of seizure in children with complex FS significantly higher than simple FS. However there was no significant difference in MPVs and PDWs between patients in the simple FS and complex FS groups at 1 month after seizure. This finding shows that more inflammatory changes occur in the acute phase of disease activity in the brain in the complex FS. Arıca et al compared the MPVs levels in children diagnosed with FMF, during attack and attack-free periods and they reported that during acute attacks, the MPV values in children with FMF were rising as the disease severity score increased[27].

Some studies showed that MPVs levels were increased due to decreased platelet count during acute infection. Therefore platelets play an important role during infection and inflammation[28,29]. Some other studies suggests that inflammation, which is intrinsic to the fever response, is involved in the generation of FS[15]. It is also reported that inflammatory cells and pro-inflammatory cytokines play significant roles in the generation of FS[16,17]. In our study, we also found that lower PLT count and increased MPV and PDW values in complex FS group and we thought that since new produced platelets are larger and more reactive because of secreted chemokines, cytokines, and other inflammatory mediators, MPV and PDW values are higher in complex FS. Therefore we speculated that the increased MPVand PDW values show the increased intensity of inflammation process in complex FS group.

It is known that chronic epilepsy syndromes, including temporal lop epilepsy with hypocampaol sclerosis associated with complex FS[15]. However the mechanisms is not yet understood, some studies suggest that inflammation might contribute to the development of temporal lop epilepsy following FS[30]. Although the sample size was small in our study, increased intensity of inflammation process in complex FS group may supports the idea which claims the association of temporal lop epilepsy and hypocampaol sclerosis with complex FS in children.

In conclusion, this is a prospective study which has evaluated the association between MPV, PDW and FS in the literature. The present study demonstrated that there was no difference in MPVs and PDWs between febrile patients with and without seizures. But this study also revealed that there was a significant difference in MPVs and PDWs between patients in the simple and complex FS groups. The increased MPV and PDW values show the increased intensity of inflammation process in complex FS group which supports the idea that claims the association of temporal lop epilepsy and hypocampaol sclerosis with complex FS. A limitation of the study was the relatively small sample size. For this reason, these findings cannot be generalized based on this study alone. Further prospective studies involving a larger patient population are needed to establish the association between MPV and PDW in patients with FS.

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