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Original Article

Mean Platelet Volume in Children with Familial Mediterranean Fever and the Relationship with Attack Status, Colchicine Treatment and Gene Mutation

Nilgun Üstün[1], Alper Murat Ulaşlı[2], Tanju Çelik[3], Erkan Yula[4], Ayşe Dicle Turhanoğlu[1]

ABSTRACT

Increased mean platelet volume (MPV) is a manifestation of platelet functions and activation, and accepted as a prognostic biomarker in patients with cardiovascular disease. We aimed to investigate MPV levels in pediatric Famillial Mediterranean Fever (FMF) patients during the attack and attack-free periods, and the effect of colchicine treatment and presence of M694V mutation. Thirty-five pediatric patients with FMF and 38 age-sex-matched healty controls were enrolled retrospectively into the study. Of the patients 11 (31%) had an ongoing attack, and 24 (69%) were in attack-free period. 26 (74%) patients were receiving colchicine and 16 (45.7%) had M694V gene mutation. There was no significant difference in platelet (PLT) and MPV between patients and healthy controls (p=0.196 and p=0.167 respectively). Mean PLT and MPV values of the patients during attack and attack-free period were also not significantly different (p=0.355 and p=0.118 respectively). However, MPV levels during an FMF attack were non-significantly lower than healthy control group (p=0.08). PLT and MPV levels were higher in patients receiving colchicine but the differences were not significant (p=0.097 and p=0.446 respectively). Mean MPV value of the FMF patients with M694V mutation was not significantly different than controls (p=0.773). In conclusion, this study reveals that pediatric FMF patients have similar MPV levels with healthy individuals even in the presence of M694V mutation. MPV as an early atherosclerosis marker, is not significantly elevated in this patient cohort. Regular treatment with colchicine and younger age may have a role in non-impaired platelet activation in FMF patients.

Key words: *Familial Mediterranean fever, MEFV gene, Mean platelet volume, Colchicine*

Ailesel Akdeniz Ateşli Çocuklarda Ortalama Trombosit Hacmi ve Atak, Kolşisin Tedavisi ve Gen Mutasyonu ile İlişkisi

ÖZET

Artmış ortalama platelet hacmi (OPH) platelet fonksiyonları ve aktivasyonunun bir göstergesidir ve kardiovaskuler hastalalığı olanlar için bir prognostik faktor olarak kabul edilmektedir. Pediatrik Ailesel Akdeniz Ateşi (AAA) hastalarında OPH düzeylerinin atak sırasında ve atak dışı dönemde incelemeyi ve kolşisin tedavisi ile M694v mutasyonunun varlığının OPH üzerine etkisini incelemeyi amaçladık. Çalışmaya retrospektif olarak 35 pediatrik yaş grubu AAA hastası ile 38 yaş ve cinsiyet eşleştirilmiş sağlıklı control grubu alındı. Çalışmaya alınan hastaların 11'inde (%31) devam eden atak mevcut iken, 24'ü (%69) atak dışı dönemdeydi. 26 (%74) hasta kolşisin tedavisi alırken, 16 (%45.7) hasta M694V gen mutasyonu taşıyordu. Hastalar ile kontrol grubu arasında platelet ve OPH bakımından anlamlı farklılık yoktu. (sırasıyla p=0.196 ve p=0.167). Ortalama platelet sayısı ile OPH değerleri atak sırasında ve atak dışı dönemde de anlamlı farklılık göstermedi (sırasıyla p=0.355 ve p=0.118). Bununla birlikte, OPH düzeyleri AAA atağı sırasında sağlıklı kontrol grubuna göre anlamlı olmayan düzeyde daha düşüktü. (p=0.08). Kolşisin tedavisi alan hastalarda platelet ve OPH düzeyleri daha yüksek idi fakat istatistiksel olarak anlamdı düzeyde değildi. (p=0.097 ve p=0.446). M694V mutasyonu taşıyan AAA'li hastaların OPH düzeyi ortalaması kontrollerden farklı değildi (p=0.773). Sonuç olarak bu çalışma pediatrik AAA hastaları M694V mutasyonu varlığında dahi sağlıklı bireylerle benzer OPH düzeylerine sahip olduğunu göstermiştir. Atherosklerozun erken bir belirteci olarak OPH bu hasta kohortunda anlamlı düzeyde artış göstermemektedir. Düzenli kolşisin tedavisi ve genç yaş AAA hastalarında platelet aktivasyonunun sağlam kalmasında rol oynayabilir.

Anahtar kelimeler: *Ailesel akdeniz ateşi, MEFV geni, ortalama platelet hacmi, kolşisin*

Mustafa Kemal University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation[1], Pediatric[3] and Microbiology[4], Hatay, Turkey, [2]Afyon Kocatepe University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Afyonkarahisar, Turkey

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Correspondence: *Nilgün Üstün*
Mustafa Kemal Ü Tıp Fak. FTR AD, Hatay, Türkiye
Tel: *+90 505 484 8487*
E-mail: *drnustun@yahoo.com.tr*

INTRODUCTION

Familial Mediterranean fever (FMF) is a common inherited autoinflammatory disorder characterized by recurrent episodes of serositis and arthritis, which are usually accompanied with fever (1). Elevation of acute phase reactants during FMF attacks as well as attack-free periods is well documented in the literature (2). The disease mainly affects Sephardi Jews, Turks, Armenians and Arabs (1). In recent years it was shown that subclinical inflammation persisted during attack free period in FMF patients (3-5). However, the long term effects with regards to ongoing inflammation are not clearly investigated yet.

Mean platelet volume (MPV) has been proposed as an indirect marker of increased platelet reactivity (6,7). Larger platelets were found to be more reactive and produce more trombotic factors such as thrombaxane A2 (8,9). High-grade inflammatory diseases, such as rheumatoid arthritis and psoriasis present with high levels of MPV, which reverse in the course of anti-inflammatory therapy (10,11). Increased MPV is a manifestation of platelet functions and activation, and accepted as a prognostic biomarker in patients with cardiovascular disease (12-14). Chronic systemic inflammation may, at least in part, contribute to formation and progression of atherosclerotic plaque and cardiovascular involvement (15,16).

The increase in atherosclerosis risk in FMF patients was reported in a few recent studies (17-19). However, there are a few studies investigating MPV levels in FMF patients (20-22).

FMF patients with M694V mutation were reported to have a more severe disease course with increased arthritis incidence and increased risk of amyloidosis. Very recently, Ahsen et al. (23), reported high neutrophil-to-lymphocyte ratio (NLR) indicating subclinical chronic inflammation in FMF patients especially carrying M694V mutation. Therefore, in this study, we aimed to investigate MPV levels in pediatric FMF patients during the attack and attack-free periods, and the effect of colchicine treatment and presence of M694V mutation.

MATERIALS AND METHODS

In the current study the computerized hospital records of the patients diagnosed with FMF who admitted to the outpatient clinics between June 2011 and July 2012 were retrospectively reviewed. The patients with complete clinical data including symptoms, past medical history, laboratory records (Complete blood count (CBC), CRP, platelet count (PLT) and MPV) could be obtained were enrolled. Demographic data, FMF gene mutation, colchicine use were also recorded for each patient. The exclusion criteria were presence of active infectious disease, diabetes mellitus, connective tissue disease, asthma, hematological disorder, renal and hepatic failure. The patients were divided into subgroups regarding attack status, treatment received and presence of M694V mutation. Patients who had the last attack at least 2 weeks before were included in the attack free group.

The control group included age and sex matched healthy subjects. CBC parameters were recorded for healthy children from the same computerized database.

After collection of the blood samples in the potassium-ethylenediaminetetraacetic acid tubes (dipotassium EDTA tube), Mindry BC-6800 automated blood cell analyzer (P.R.C.) was used to measure complete blood count within 2 hours after veni-puncture as the laboratory policy to avoid EDTA induced swelling. The normal range of MPV values in our laboratory were between 6.5-11.6 fl. The study protocol was approved by the local ethics committee.

Statistical analysis

Statistical analysis was performed by using the SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA) for windows. Kolmogorov-Smirnov test was used to evaluate the distribution of the continuous variables. Student t test was used for comparison of parameters showing normal distribution and Mann-Whitney U test was used for comparison of parameters without normal distribution. Chi-square test was used for categorical variables. Pearson or Spearman test were used to assess the relationships where appropriate. A p value of <0.05 was considered as statistically significant.

RESULTS

The hospital records of 41 pediatric patients with FMF were retrospectively analyzed. Four FMF patients of whom all laboratory data were not obtained and two patients with renal failure were excluded. 38 age and

sex matched healty controls were included in the study. Mean age of the patients was 8.80±3.32 years. Of the patients 11 (31%) had an ongoing attack, and 24 (69%) were in attack-free period. 26 (74%) patients were on colchicine treatment. 16 (45.7%) patients had M694V gen mutation.

Mean CRP was 0.91±2.33 mg/L (normal ≤ 0.8 mg/L). There was no significant difference in mean CRP levels between FMF patients during attack and attack-free period (1.14±2.70, 0.82±2.23, p=0.728 respectively).

Mean PLT and MPV values of the patients and healthy controls are demonstrated in Table 1. There was no significant difference in PLT and MPV between patients and healthy controls (p=0.196, p=0.167 respectively). Mean PLT and MPV values of the patients during attack and attack-free period were also not significantly different (p=0.355, p=0.118 respectively). However, MPV levels during an FMF attack were lower than healthy control group, but the difference did not reach statistically significant level (p=0.08). PLT and MPV levels were higher in patients receiving colchicine but the differences were not significant (p=0.097, p=0.446)

Of the patients having M694V mutation, 14 were receiving colchicine therapy. Mean MPV value of the FMF patients with M694V mutation was not significantly different than healthy controls (p=0.773).

There was a non-significant inverse correlation between MPV and PLT in the patient group overall (p=0,334, r= -0.168). The correlation between MPV and PLT in the patients during attack (p=0,555, r=200); attack-free (p=0.109, r= - 336) were also non-significant. However, a significant inverse correlation was found between MPV and PLT in healthy controls (p=0,043 r= -0.330).

DISCUSSION

The main findings of the current study were; MPV values in pediatric FMF patients and healthy controls were not different. MPV values were not different between the patients during attack and attack free periods. MPV and PLT values were also not affected by colchicine treatment and the presence of M694V mutation.

Because large platelets are more active hemostatically (12-14), higher MPV levels in FMF can be associated with increased risk of atherosclerosis. Additionally, a few previous studies have shown that FMF was associated with increased atherosclerosis risk (17-19). However, according to the results of this study, MPV changes in FMF patients might not be a predisposing factor for increased atherosclerosis at least in pediatric age group. Further, in the study by Peru et al. (18), evaluating carotid intima-media thickness in children with FMF, they reported no correlation with MEFV mutation subgroups including M694V. Likewise, the MPV and PLT values were not different in patients with M694V mutation in the current study.

Makay et al. (20) reported that there was no significant difference in MPV levels between FMF patients during attack-free period and healthy controls, while significant reduction in MPV levels were detected during attacks in comparison to attack-free period. In addition, free from attack status, Abanonu et al. found no significant difference in MPV levels between FMF patients and healthy controls (21). In contrast, Sahin et al. (22) reported significantly lower MPV levels in FMF patients compared to healthy controls while there was no difference in MPV levels between FMF patients during attack and attack-free periods. In the current study, lowest MPV values were observed in patients with an acute attack and the highest MPV values were in patients with

***Table 1**. Mean platelet and MPV values of the patients and control group considering attack status and presence of M694V mutation.*

	n	*PLT*	*MPV*
All patients	*35*	*340.97±70.35*	*7.05±0.98*
During attack	*11*	*360.45±89.89*	*6.75±0.57*
Attack free	*24*	*332.04±59.48*	*7.20±1.10*
Receiving colchicine	*26*	*352.45±71.67*	*7.07±1.10*
No colchicine	*9*	*307.44±57.26*	*7.01±0.49*
M694V mutation (+)	*16*	*335.88±78.14*	*7.53±1.11*
M694V mutation (-)	*19*	*345.26±64.95*	*6.77±0.72*
Controls	*38*	*313.63±56.71*	*7.23±0.85*

PLT: platelet count (normal 142-424 x 103/μL); MPV: mean platelet me (normal 6.5-11.6 fL).

M694V mutation free from attack status. Overall, pediatric FMF patients had non-significantly lower MPV values compared to healthy controls.

Colchicine use may suppress platelet activation (24-26), and the majority of our patients were on colchicine treatment. This may partially explain the non-significant difference of PLT and MPV values between patients and healthy controls. Second, the small sample size can be counted as another limitation of the study. Third, the patients were not examined directly or indirectly with any methods to investigate atherosclerosis.

In conclusion, this study reveals that pediatric FMF patients have similar MPV levels with healthy individuals even in the presence of M694V mutation. MPV as an early atherosclerosis marker, is not significantly elevated in this patient cohort. Regular treatment with colchicine and younger age may have a role in non-impaired platelet activation in these patients.

Decleration of interests

All authors have no conflict of interest

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