

# Evaluation of the mean platelet volume in children with familial Mediterranean fever

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**Abstract** To evaluate the Mean Platelet Volume (MPV) levels in children diagnosed with familial Mediterranean fever (FMF), during attack and attack-free periods. The records of a total of 117 children with FMF, diagnosed using the Tel-Hashomer criteria, have been scanned. The study consisted of 53 patients during an attack (group 1), 64 patients in attack-free period (group 2), and 57 healthy controls (group 3). Erythrocyte sedimentation rate, C-reactive protein, white blood cell count, platelet count, and MPV levels were retrospectively recorded. The MPV and platelet values in FMF patients during attack (group 1) and FMF patients during attack-free periods (group 2) have been found to be significantly higher than those of the health control group (group 3). Positive correlation has been found between the MPV and platelet values in Group 1 and the disease's severity score ( $r = 0.224$ , and  $r = 0.268$ , respectively). Positive correlation ( $r = 0.528$ , and  $r = 0.485$ , respectively) has been also identified between MPV and blood platelet count in patients in Group 1 and 2.

No correlation was found between the Colchicine treatment period and MPV ( $r = -0.005$ ). The MPV values in the complete group of FMF diagnosed children have been found to be much higher compared to those in healthy children. As a consequence, we consider the MPV value as a useful marker that demonstrates the risk of early stage atherosclerosis in children with FMF.

**Keywords** Familial Mediterranean fever · Atherosclerosis · Mean Platelet Volume · Platelet

## Introduction

Familial Mediterranean fever (FMF) is a recurrent, autosomal, and recessive auto-inflammatory disease characterized with various serosal forms in which fever accompanies pain in the abdominal area, chest, and joints [1, 2]. The disease is common among Mediterranean societies incl. Turks, Armenians, Jews, and Arabs [3]. Male/Female ratio as 1.20/1 is in favor of the male population [4]. Nowadays, the disease is diagnosed using clinical findings and family history together with molecular scan. Tel-Hashomer is the most frequent among the various criteria developed for diagnosis [5]. Acute phase reactants increase during FMF attacks [6]. Although not capable to completely block the attacks, Colchicine treatment has been definitively shown to prevent amyloidosis in many FMF patients [7]. The long-term effects of sub-clinical inflammation in children with FMF have not been clarified to a complete extent. The few number of studies performed in this area suggest the increase of atherosclerosis as the long-term effects of this auto inflammation [8–11].

During atherogenesis, platelet aggregation and migration of smooth muscle cells from the media to endothelium and consequent proliferation are the early events [12].

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The results of the measurement of carotid intima media thickness made in order to determine atherosclerosis in patients with FMF yielded inconsistent results [9–11, 13]. The Mean Platelet Volume (MPV) is an indicator of platelet activation. Blood platelet dimension is associated with the thrombocyte function and activation [14]. Thus, MPV as a marker of platelet activation is used as an indicator of atherosclerosis.

There are 2 studies that review MPV measurement in FMF patients in the literature [15, 16]. Our study is valuable due to its review conducted on children with FMF, acute attack patient group, and the large number of pediatric patients.

## Materials and methods

The records of the cases we had diagnosed with FMF and monitored at the pediatric clinic of the School of Medicine of the Mustafa Kemal University (Hatay, Turkey) between November 2009 and May 2011 have been reviewed retrospectively.

All patients were diagnosed according to Tel-Hashomer criteria [5]. All subjects were receiving Colchicine treatment. A total of 117 records of the cases diagnosed with FMF in the 0–15 age range have been searched. The cases in the study have been categorized as 3 groups. Group 1 included the cases diagnosed with FMF and with ongoing attack (n:53), Group 2 involved individuals diagnosed with FMF, but were attack free (n:64) (with a period of at least 2 weeks since the latest attack), and Group 3 was the control group (n:57). Demographic data, starting age, the period between ages of onset of the diseases and diagnosis, diseases severity score, FMF gene mutations, Colchicine dose, and treatment periods have been taken under record for each patient.

The data have been collected using the electronic patient database of the patient's latest visit. Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), White Blood Cell Count (WBC), number of platelets (PLT), and Mean Platelet Volume (MPV) data have been recorded. Full blood count parameters have been recorded for healthy children on the same computer database. Full blood count analyses are performed using the Coulter analyzer in our institution's central laboratory. The standard tubes subjected to full blood count contained ethylenediaminetetraacetic acid in certain amounts.

## Statistical analysis

Data were evaluated using the Statistical Package for Social Sciences 16.0 program for Windows and by analyzing descriptive statistics (means and standard deviation),

comparing the means of quantitative data for more than two groups with Kruskal–Wallis test and by comparing dual groups using the Student's *t* test. *P* value <0.05 was considered as significant. Intercorrelations between parameters were computed through the Pearson's correlation analysis.

## Results

Twenty-eight out of total 53 cases in Group 1 were male and 25 were female. 35 of the 64 cases in total in Group 2 were male and 29 were female. 30 of the 57 cases in Group 3 were male while 27 were female. The groups did not differ in terms of the number of individuals based on their gender. The average onset age of the disease was  $3.8 \pm 2.3$  years in Group 1, while it was  $4.4 \pm 2.7$  years in Group 2. There was no significant difference between the Groups ( $P = 0.32$ ). Average age for diagnosis was  $8.1 \pm 4.7$  years for Group 1 and  $8.3 \pm 4.3$  years for Group 2. There was no significant difference between the groups ( $P = 0.14$ ). The average period between the onset of symptoms and diagnosis was  $2.8 \pm 2.5$  years for Group 1 and  $3.2 \pm 3.0$  years for Group 2. There was no significant difference between the groups ( $P = 0.21$ ). The average Colchicine dose administered was  $1.1 \pm 0.7$  mg/kg in Group 1 and  $1.1 \pm 0.5$  mg/kg in Group 2. There was no significant difference between the groups ( $P = 0.75$ ) (Table 1).

The gene analysis of children with FMF demonstrated a number of M694V homozygosis as 37 (58%) in group 1 and M694V homozygosis number of 47 (56%) for group 2. There was no statistical difference between 2 groups ( $P = 0.64$ ).

The Mean Platelet Volume (MPV) and platelet values of attacked attack (group 1) and attack-free FMF patient groups (group 2) have been found to be significantly higher than those in the healthy control group (group 3). Although there was no difference of statistical importance between the MPV and blood platelet values in Group 1 and 2, the number of MPV values in group 1 was higher than that in group 2. C-reactive protein (CRP), sedimentation (ESR), and leukocyte (WBC) values were significantly higher in the FMF group under attack (group 1) compared to group 2 and 3. No significant difference was found between the Groups 2 and 3 (Table 2).

No cases with a blood platelet count less than 150.000/ $\mu$ l and higher than 400.000/ $\mu$ l have been identified in the healthy group and both FMF groups. Mean Platelet Volume was lower than normal (<7.0 fl) in 4 of 53 patients in attack and 5 of 64 patients without attack. None of the healthy controls had low MPV.

Positive correlation has been found between the MPV and platelet values in Group 1 and the disease's severity

**Table 1** Demographic characteristics of FMF patients

Parameter	Group 1 (n:63)	Group 2 (n:84)	P value
Gender (M/F)	33/30	45/39	0.79
Age at onset (years)*	3.8 ± 2.3	4.4 ± 2.7	0.32
Age at diagnosis (years)*	8.1 ± 4.7	8.3 ± 4.3	0.14
Delay in diagnosis (years)*	2.8 ± 2.5	3.2 ± 3.0	0.21
Colchicine dose (mg/day)*	1.1 ± 0.7	1.1 ± 0.5	0.75

\* Mean ± SD

**Table 2** Comparison of blood count parameters among the groups

Parameter	Group 1 (n:53)	Group 2 (n:64)	Group 3 (n:57)	Group comparisons (P value)*
MPV (fl)	8.3 ± 0.6	8.1 ± 0.4	7.4 ± 0.3	1–2 (0.34), 1–3 (0.01), 2–3 (0.02)
PLT (×103/μl)	354 ± 45	347 ± 48	265 ± 97	1–2 (0.85), 1–3 (0.01), 2–3 (0.02)
WBC (×103/μl)	12.4 ± 6.3	7.2 ± 3.1	7.4 ± 2.9	1–2 (0.00), 1–3 (0.00), 2–3 (0.44)
CRP (mg/l)	45 ± 24.7	4.1 ± 3.4		1–2 (0.00)
ESR (mm/h)	37.7 ± 13.0	11.2 ± 7.4		1–2 (0.00)

Values are given as mean ± SD

\* P &lt; 0.05 is significant

score ( $r = 0.224$ , and  $r = 0.268$ , respectively). Positive correlation has been also found between MPV and platelet counts in Group 1 and Group 2 ( $r = 0.528$ , and  $r = 0.485$ , respectively). Positive correlation has been found between the CRP and ESR values in Group 1 ( $r = 0.442$ , and  $r = 0.486$ , respectively). No correlation has been found between the period of Colchicine administration and MPV ( $r = -0.005$ ).

## Discussion

Familial Mediterranean fever (FMF) is a recurrent, autosomal, and recessive auto-inflammatory disease characterized with various serosal forms in which fever accompanies pain in the abdominal area, chest, and joints [1, 2]. While not universal, it is a disease based on ethnic origin. The disease is 1/1,000 prevalent in Turkey and the carrier ratio is 1/5 [15].

The literature contains only 2 studies which describe the relationship between FMF and MPV [16, 17]. Both studies originate from Turkey as FMF is more frequent, particularly the Mediterranean region situated in the southern territory of our country. This study has been conducted in the Hatay province situated in this region.

Our study found that the MPV values of patients diagnosed with FMF (group 1 and group 2) were higher compared to healthy children (group 3). In addition to the foregoing, we found a positive correlation of MPV and platelet counts between both groups of FMF diagnosed children (group 1 and group 2). Coban et al. found that the MPV values of attack-free FMF patients were higher compared to those of healthy individuals [16]. This suggestion was concordant to our study. However, they did not measure the MPV values of FMF patients during the

attacks but studied the patients with FMF as a single group. Our study is a different and valuable endeavor in such terms. Although our study yielded a higher average of MPV values in the FMF group compared to healthy children, the MPV values measured during the attack were larger in number. However, during the second study conducted in our country, Makay et al. [17] categorized the FMF patient group in two categories (group 1 under attack and group 2 attack free). The MPV values of the attack-free FMF patients were found surprisingly less compared to those of healthy individuals.

Large platelets are more active hemostatically [14, 18]. There are studies suggesting that high MPV values increase the risk of atherosclerosis [8–11, 19]. We suggest that we could demonstrate the future risk of atherosclerosis by keeping track of the MPV values of children diagnosed with FMF. On the other hand, the studies conducted by Sari et al. [13] and Seyahi et al. [20] did not find a significant difference through the ultrasonographic measurement of the carotid intima thickness of FMF diagnosed patients and comparison of the results with the control group. They demonstrated that this method was not useful in the early detection of the risk of atherosclerosis in patients diagnosed with FMF. Therefore, our study suggests that MPV value is an important marker in terms of identifying the risk of atherosclerosis in FMF diagnosed patients at an early stage. We demonstrated that even a simple full blood count could determine the risk. Risk of atherosclerosis can be proposed through the review of the MPV value with no need for a supplemental blood test or radiology examination.

The risk of atherosclerosis increases with age [12]. Since our patient group diagnosed with FMF is at the childhood stage, proposing the risk of future atherosclerosis is important for taking the required measures.

Peru et al. suggested that the risk of atherosclerosis in FMF patients may depend on environmental factors [10]. The studies performed in different regions and yielding different results imply that the risk of developing atherosclerosis in FMF patients might be associated with different lifestyles and social-economical conditions.

Our study identified positive correlation between the MPV values, platelet counts, and the disease severity score of children with FMF under acute attack. We also found that during acute attacks, the MPV values in children with FMF were rising as the disease severity score increased. This correlation was not present in the acute attack-free FMF patient group. The increase suggests the presence of several cytokines during the attack, which suggests a possible change in the platelet volume. During the studies, the increase in the interleukin-6 (IL-6) level during acute attack of the FMF patients was shown [6, 21, 22]. There are studies which demonstrate that IL-6 as an important pro-inflammatory cytokine might affect the platelet volume [23, 24]. However, we think that increased IL-6 level alone is not the only factor that changes the platelet number and volume since we also found that the MPV and platelet numbers in the FMF patient group during the attack-free phase were high. In addition to IL-6, we suggest that these events are promoted by further factors which are not yet known. We suggest that together with the inflammatory effect, the high value of MPV and platelets during acute attacks would increase the frequency of atherosclerosis during the future years.

No correlation has been found between the period of Colchicine administration and MPV. This suggests that Colchicine alone is not capable to prevent the development of atherosclerosis. However, we could have compared the MPV and platelet counts with the FMF group on Colchicine if we had an FMF group that was not using the drug. Yet, we had no FMF pediatric patient who was not administered Colchicine. This effect can be researched during prospective studies at a later stage.

In conclusion, we found that the MPV values in the complete group consisting of children with FMF were higher than those in healthy children. We think that this could be useful as marker demonstrating the risk of atherosclerosis in children with FMF at the early stage. We should evaluate the MPV values in FMF patients, and particularly, children subject to frequent acute attacks in order to take the required measures to prevent the risk of atherosclerosis.

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